EXHIBIT 1

Exhibit 2

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	No. 1:19-md-2875-RBK

Expert Report of Fengtian Xue, Ph.D.

December 22, 2022

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I. Overview And Summary Of Opinions

I have been retained by counsel for Zhejiang Huahai Pharmaceutical Co. ("ZHP") to offer expert opinions regarding whether, from an organic-chemistry perspective: (1) ZHP conducted adequate and appropriate risk assessments, prior to making various changes to the manufacturing process for its Valsartan active pharmaceutical ingredient ("API") over time; (2) ZHP conducted adequate and appropriate testing of its Valsartan API during the time period that the API was available to customers in the United States; (3) ZHP knew, or reasonably should have known, that any of the manufacturing processes it used to create Valsartan API could result in the formation of N-nitrosodimethylamine ("NDMA") or N-nitrosodiethylamie ("NDEA"); and (4) ZHP acted appropriately in responding to reports of NDMA/NDEA in its Valsartan API.

As part of this assignment, I have been asked to review and comment on opinions that have been offered by various experts retained by the plaintiffs in this litigation, including Stephen Hecht, Ph.D.,[1] Ron Najafi, Ph.D.,[2] Laura Plunkett, Ph.D.[3] and Susan Bain, DRSc,[4] to the extent those opinions relate to the scope of my work described above.

My opinions are based on my significant knowledge, training, research and experience in the field of Organic Chemistry and Medicinal Chemistry, including with respect to the potential formation of carcinogens as a chemical process. A complete list of the materials that I reviewed and considered in forming my opinions is set forth in **Exhibit A** to this report. I also spoke with three ZHP employees: Min Li, Jucai Ge and Jinsheng Lin.

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[1] Expert Report of Stephen S. Hecht, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, July 6, 2021; Expert Report of Stephen S. Hecht, Ph.D, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022 ("2022 Hecht Rep.").

[2] Expert Declaration of Ron Najafi, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, November 4, 2021; Expert Report of Ron Najafi, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022 ("2022 Najafi Rep.").

[3] Expert Report of Laura M. Plunkett, Ph.D., DABT, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022("Plunkett Rep.").

[4] Expert Report of Susan Bain, DRSc, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022 ("Bain Rep.").

As set forth in greater detail below, I intend to offer the following opinions in connection with this case.

- ZHP performed reasonable and appropriate scientific risk assessments regarding the relevant manufacturing processes it used to create its Valsartan API given the information reasonably available in the field of organic chemistry at the time;
- ZHP performed reasonable and appropriate scientific testing of its Valsartan API for potential impurities during the time that its Valsartan API was available on the market; and
- ZHP did not know, and could not have been reasonably expected to know, that the manufacturing processes for its Valsartan API could result in the formation of NDMA or NDEA until it was alerted to the presence of these impurities in its Valsartan API by customer Novartis in 2018.

I hold these opinions and those set forth below to a reasonable degree of scientific certainty.

II. Qualifications

I received my B.S. in Chemistry in 2001 from the University of Science and Technology of China. During the five years of my undergraduate training, I received multiple awards, including the Xu-Xin Fellowship (1997), the Japan Shi-Ye-Tong-Xun-Wang Fellowship (1998), and the USTC First Prize of Excellent Undergraduate Scholarship (1999, 2000, 2001). I was also the recipient of the Outstanding College Student of the Year for Anhui Province (2001).

In April 2007, I obtained my Ph.D. in Chemistry from Brown University. While I was pursuing my doctorate degree, I worked as a Teaching Assistant for five years and supervised more than 100 undergraduate students in General Chemistry and Organic Chemistry Labs from 2001 to 2005. At Brown University, my thesis research focused on small-molecule anti-cancer therapeutics by targeting the serine protease plasmin. During my time at Brown University, I published seven research articles and was the first author for five of those articles. Such publications include the 2005 article entitled: "A Comparison of Cyclohexanone and Tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide as Pharmacophores for the Design of Peptide-Based Inhibitors of the Serine Protease Plasmin" in *The Journal of Organic Chemistry*. The article reported the design, organic synthesis, and in vitro tests of three pairs of novel compounds as potential inhibitors of the

serine protease Plasmin. Some of the target molecules synthesized required more than 10 steps of organic synthesis. In the same year, I published "Selective Inhibitors of the Serine Protease Plasmin: Probing the S3 and S3' Subsites Using a Combinatorial Library" in the *Journal of Medicinal Chemistry*. In connection with this work, I synthesized and tested a 400-peptide library to identify new drug-like small molecule inhibitors of Plasmin and routinely used the organic solvent Dimethylformanide ("DMF") in my synthesis. I also published "Structure-Activity Studies of Inhibitors for the Serine Protease Plasmin: Design, Synthesis, and Biological Activity" in *Bioorganic Medicinal Chemistry*, "Macrocyclic Inhibitors of the Serine Protease Plasmin" in *Journal of Enzyme Inhibition and Medicinal Chemistry*, and "Fluorescent Probes to Study Serine/Threonine Phosphatase" in *Organic Letters*. I presented my research results five times at the National Meetings of the American Chemical Society. During my last year at Brown University, I was honored as the recipient of the Graduate Dissertation Fellowship.

From 2007 to 2009, I completed postdoctoral training at Northwestern University in Professor Richard B. Silverman's laboratory. My postdoctoral research focused on the synthesis and characterization of small molecule inhibitors for neuronal nitric oxide synthase (nNOS). nNOS is an enzyme that produces nitric oxide (NO), which can be converted into nitrosonium ion (NO^+) by losing one electron. Because of the nature of this project, I gained significant expertise regarding the production and reactivity of NO and other reactive nitrogen species ("RNS") including NO^+, which is a key reactant for the reactions leading to the formation of nitrosamines (e.g., NDMA and NDEA), as described below. During this two-year period, I successfully collected enough data to publish 15 research articles (eight first authors and seven coauthors). In addition, I was listed as an inventor on six patent applications.

From 2009 to 2011, I served as an Assistant Professor in the Department of Chemistry at the University of Louisiana at Lafayette, teaching Organic Chemistry and Organic Chemistry Lab courses that were required for all chemistry major and pre-med undergraduate students. As a result of this teaching experience, I have substantial expertise regarding the information that was common knowledge in the Organic Chemistry and Medicinal Chemistry fields, and what was included in Organic Chemistry textbooks, during that time period.

In August 2011, I started my independent research lab at the University of Maryland Baltimore, where I currently serve as an Associate Professor in the Department of Pharmaceutical

Sciences. My laboratory has a broad interest in the development of small molecule therapeutics for important human diseases, including cancer (*see, e.g.*, *Cell Report* 2013, *Org. Lett.* 2015, *J. Clin. Invest.* 2016, *J. Org. Chem.* 2017, *Org. Biomol. Chem.* 2017, *J. Med. Chem.* 2018 2019 2021, *ACS Med. Chem. Lett.* 2019, *JCI Insight* 2022, *Bioorg. Med. Chem.* 2022), infections (*see, e.g.*, *Tetrahedron Lett.* 2013 2022, *J. Med. Chem.* 2013 2016, *Bioorg. Med. Chem. Lett.* 2018, *J. Biol. Inorg. Chem.* 2018, *Microb. Pathog.* 2019, *ACS Infect. Dis* 2020, *Front. Microbiol.* 2021, *Biochemistry* 2021), metabolic disorders (*see, e.g.*, *Mol. Pharm.* 2017, *J. Med. Chem.* 2019), and neurodegenerations (*see, e.g.*, *Hum. Mol. Genet.* 2014, *Tetrahedron Lett.* 2014, *Bioorg. Med. Chem.* 2015, *Bioorg. Med. Chem. Lett.* 2015, *PloS One* 2015). Our research projects have been supported by government agencies (e.g., National Institutes of Health ("NIH") and National Science Foundation ("NSF")), prominent cancer research foundations (e.g., American Association for Cancer Research ("AACR") and Leukemia Research Foundation), and industry (e.g., Janssen Pharmaceuticals).

I have been a member of the American Chemical Society since 2001. I am also a member of Sigma Xi, the American Association for the Advancement of Science, the American Association of Colleges of Pharmacy, the American Association of Pharmaceutical Scientists, and the AACR. I am an active reviewer for 37 peer-reviewed journals and have served on NIH study sections as an expert for grant review. To date, I have published more than 85 research articles in the fields of Organic Chemistry and Medicinal Chemistry. Also, I am an inventor of more than 20 patents and patent applications on novel discoveries of novel synthetic methodologies and small molecule therapeutics. As an Organic/Medicinal Chemist for more than 20 years, I have broad training in organic synthesis, medicinal chemistry, and drug discovery, with specific training and expertise in designing, synthesizing, and biological characterization of small molecule therapeutics.

A copy of my Curriculum Vitae (CV) with a complete listing of my educational, teaching, scholarship, and service activities, is attached as **Exhibit B**. I am being compensated at the rate of $300 per hour. My compensation is not contingent upon the outcome of this case or litigation.

III. Overview Of ZHP's Manufacturing Processes For Valsartan API

From 2007 to 2018, ZHP employed four distinct manufacturing processes to produce the Valsartan API used to produce Valsartan-containing drugs ("VCDs"). This section provides a brief overview of those processes and when they were developed and used.

A. The "Tin Process" – DMF No. 020939

ZHP submitted a Drug Master File[5] (DMF #020939) regarding the first process it used to produce Valsartan API ("Process I," or the "Tin Process") on September 24, 2007.[6] In the Tin Process, the crude Valsartan (step #4) for the Valsartan API was produced via the following chemical processes (**Figure 1**). First, the *CN*-starting material was treated with sodium azide (NaN_3) to form the tetrazole compound in the presence of a catalyst tributyltin chloride (Bu_3SnCl), using xylene as a solvent. Then, saponification of the methylester in KOH using xylene yielded the carboxylate crude product. Finally, the crude product was acidified by aqueous HCl and purified by crystallization using ethyl acetate.

Tin Process, crude Valsartan (step #4)

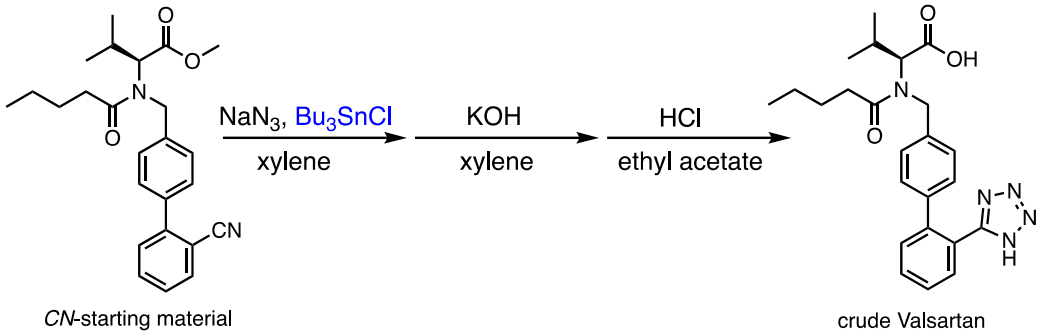

Figure 1. The crude Valsartan (Step #4) of the Tin process at ZHP.

B. The "TEA Process" – DMF No. 023491

On January 22, 2010, ZHP filed its original paper submission with the FDA regarding the second process it used to produce Valsartan API ("Process II" or the "TEA Process").[7] On February 16, 2010, the FDA assigned DMF No. 023491 to Process II.[8] The TEA Process used

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[5] "Drug master files (DMFs) are submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products." U.S. FDA, Drug Master Files (DMFs) (current as 10/24/2022) (available at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs). "FDA reviews the technical contents of DMFs in connection with the review of applications that reference them (e.g., NDAs, ANDAs, INDs, BLAs)." *Id*.

[6] (ZHP01660190; ZHP02642306; ZHP01660191; ZHP01661566; ZHP01660621; ZHP01661804; ZHP01661581; ZHP01660223; ZHP01660321; ZHP01661736; ZHP01660345; ZHP01660532; ZHP01660583; ZHP01661835; ZHP01661845; ZHP01660092; ZHP01661847; ZHP01661882; ZHP01662029; ZHP01662062; ZHP01662097.)

[7] (PRINSTON00000008; ZHP01458188.)

[8] (SOLCO00032578.)

triethylamine ("TEA") hydrochloride salt (TEA•HCl) as the catalyst for tetrazole formation in the crude Valsartan (step #4) of the Valsartan manufacturing process (**Figure 2,** top), instead of Bu_3SnCl.[9] It also replaced xylene with toluene as a solvent.[10] In the TEA process, the TEA•HCl is used as the catalyst to avoid the usage of metal-based catalyst Bu_3SnCl. This eliminates the concern of removing the residual amount of metal tin during the production of Valsartan. Also, the new catalyst TEA•HCl is more cost-efficient than Bu_3SnCl.[11]

C. The "TEA Process With Quenching" – Amendment-002 To DMF No. 023491

On April 16, 2012, ZHP submitted Amendment-002 to DMF No. 023491 ("Amendment-002").[12] Amendment-002 added a quenching procedure after the tetrazole formation reaction in the crude Valsartan (step #4) of the Valsartan manufacturing process (**Figure 2**, middle) using sodium nitrite ($NaNO_2$)/HCl solution.[13] The molar ratio for the sodium azide (NaN_3) used in the reaction was decreased from 2 to 1.5, although still excess.[14] Amendment-002 also involved the replacement of potassium hydroxide (KOH) with sodium hydroxide (NaOH) in the saponification process.[15]

The quenching process using a $NaNO_2$/HCl solution was added to destroy the excess NaN_3 used in the tetrazole formation reaction and minimize the risk of Environment, Health & Safety (EHS) concerns during manufacturing with respect to the possibility of residual azide in the final drug substance.[16] In addition, the change of molar ratio of raw starting material to NaN_3 (from 2:1 to 1.5:1) was made to decrease the formation of the impurity D-Valsartan.[17] Finally, the change

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[9] (ZHP01710671.)

[10] ZHP received a deficiency letter from the FDA regarding DMF No 023491 on October 27, 2010 (the "October 2010 Deficiency Letter"). (PRINSTON00070492-00070494.) On February 4, 2011, ZHP provided response to the October 2010 Deficiency Letter, which included Amendment-001 to DMF No. 023491 ("Amendment-001"). (PRINSTON00070492-00070569.) Amendment-001 responded to the October 2010 Deficiency Letter's concerns.

[11] (ZHP01710671.)

[12] (PRINSTON00079747-PRINSTON00079755.)

[13] (PRINSTON00079751.)

[14] (PRINSTON00079752.)

[15] (*Id.*)

[16] (PRINSTON00079752.)

[17] This belongs to a type of organic reaction named racemization (**Figure S1**), in which the orientations of two chemical bonds (highlighted in red) are inverted. Racemization results in formation of the impurity D-Valsartan.

of KOH to NaOH in the saponification process was a non-functional replacement intended to address the cost of the manufacturing process.[18]

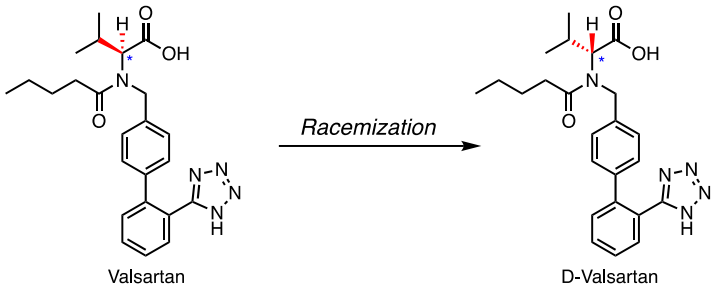

Figure S1. Formation of the impurity D-Valsartan through the racemization reaction of Valsartan. The reaction center is labeled by "*". The chemical bonds that are inversed during the reaction are shown in red.

Following the implementation of the changes set forth in Amendment-002, ZHP distinguished the TEA Process into two subcategories—"without quenching" (original "Process II" prior to Amendment-002) and "with quenching," which referred to product made using the process identified in Amendment-002.[19]

D. The "Zinc Chloride ($ZnCl_2$) Process" – Amendment-004 To DMF No. 023491

On December 10, 2013, ZHP submitted Amendment-004 to DMF No. 023491 ("Amendment-004").[20] Amendment-004 changed the catalyst reagent amine salt TEA•HCl to $ZnCl_2$ for the tetrazole formation in the crude Valsartan (step #4) and changed the solvent toluene to dimethylformamide (DMF) for the tetrazole formation reaction (**Figure 2**, bottom).[21] Amendment-004 also changed the crude Valsartan (step #4) of the manufacturing process such that, after the tetrazole reaction, quenching occurred in the presence of a newly-added solvent methyl tertiary butyl ether ("MTBE"), providing better solubility for the in-situ intermediate to

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[18] (*Id.*)

[19] (PRINSTON00079751.) On March 1, 2013, ZHP submitted its Annual Report to the SEC as well as Amendment 003 to DMF No. 023491 ("Amendment 003"). (PRINSTON00000009; PRINSTON00072212 and PRINSTON00072213-PRINSTON00072225.) The change summary in the Annual Report noted that while Amendment 003 proposed several changes to the equipment used in the manufacturing process, and a non-substantive format change to the product's label, "the manufacturing process ha[d] not changed." (PRINSTON00072212.)

[20] (PRINSTON00000009; PRINSTON00073120; PRINSTON00073102-PRINSTON00073119.)

[21] (PRINSTON00073104-PRINSTON0073108.)

avoid emulsification disturbing the liquid delamination and separation processes.[22] Following Amendment-004, ZHP's manufacturing process for Valsartan API was as follows (**Figure 2**, below):

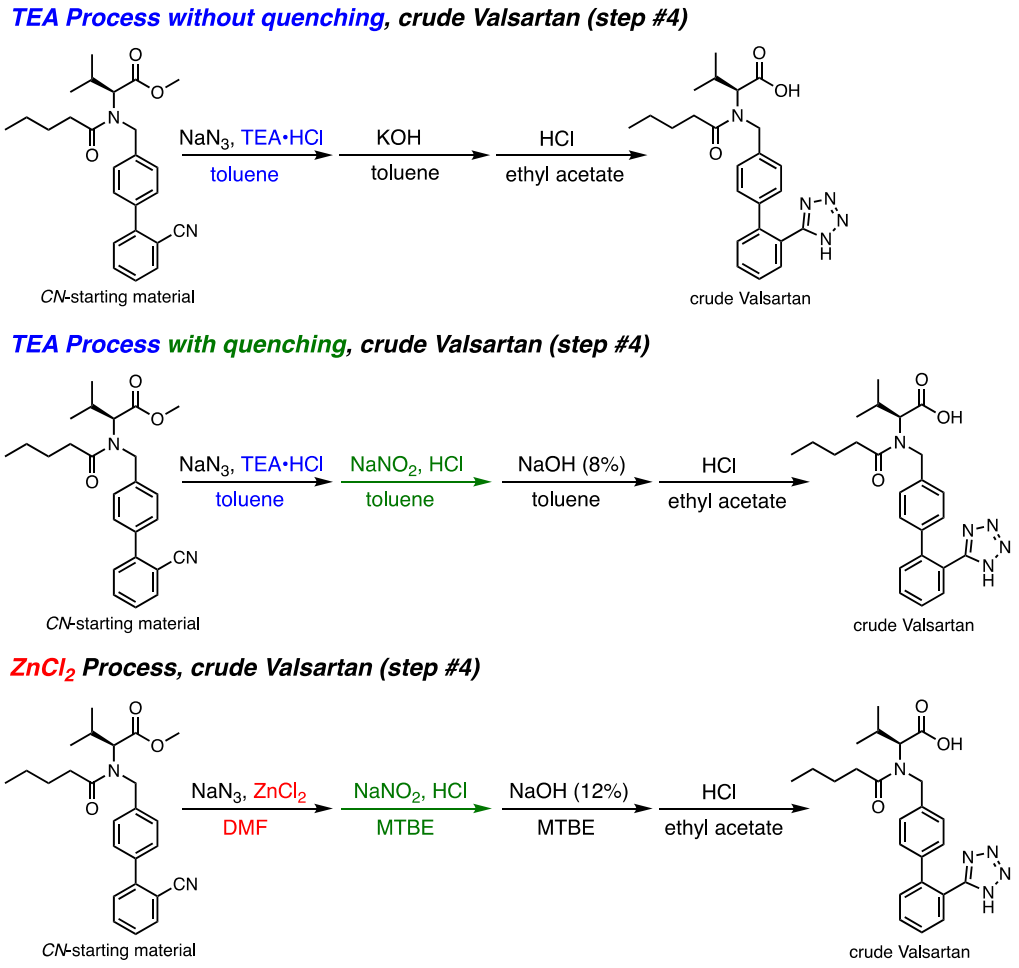


Figure 2. Comparison of the TEA process without quenching (top), TEA process with quenching (middle), and $ZnCl_2$ process (bottom) for the crude Valsartan step (#4).

Per ZHP documents, the usage of $ZnCl_2$ as a catalyst in the tetrazole formation reaction of the crude Valsartan (step #4) yielded a dramatic improvement in the conversion of the tetrazole formation reaction and significantly increased the crude process output.[23] In addition, optimization of the hydrolysis process in the crude Valsartan (step #4) not only helped to decrease

[22] (PRINSTON00000005-PRINSTON00000006.)

[23] (PRINSTON00074781.) [Chinese]

the formation of the impurity D-Valsartan (**Figure S1**),[24] but also helped to minimize the remaining of the unhydrolyzed Valsartan methylester in the crude Valsartan (step #4) (**Figure S2**) and, as a result, provided a better overall yield of the reaction.[25]

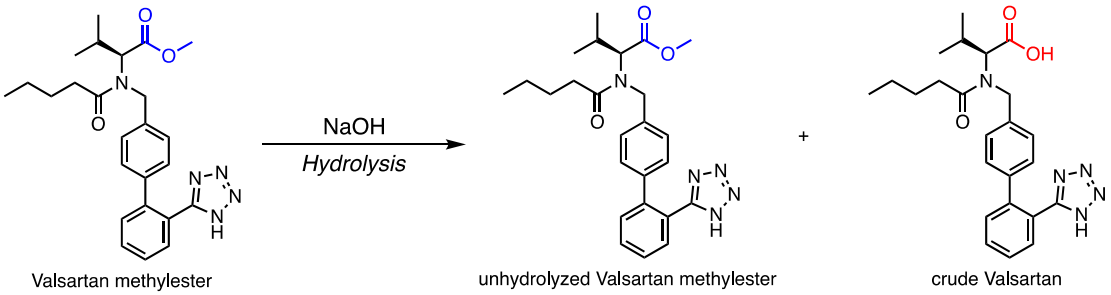
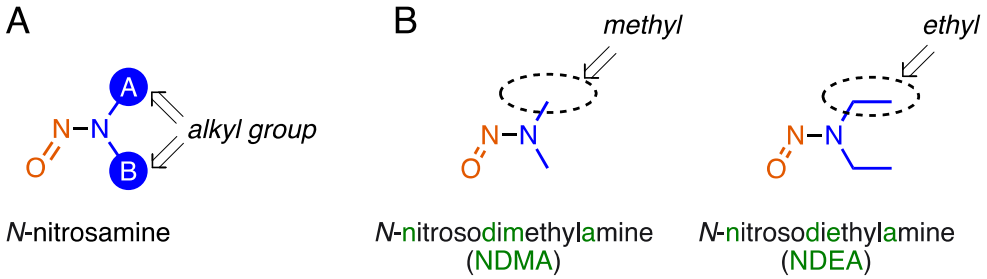


Figure S2. Under the NaOH-mediated hydrolysis conditions, some Valsartan methylester cannot be converted into the crude Valsartan and remains in the reaction mixture as unhydrolyzed Valsartan methylster. The ester group in the Valsartan methylester starting material and unhydrolyzed Valsartan methylester are shown in blue. The hydrolyzed product (-COOH) is shown in red.

IV. Overview Of Nitrosamines And Nitrosamine Formation

Nitrosamines (general structure shown in **Figure 3A**) are organic molecules with a nitroso group (**Figure 3A**, orange) connected to a deprotonated amino group (**Figure 3A**, blue) through a single bond (**Figure 3A**, black line between the two N atoms). "A" and "B" are both alkyl groups, referring to organic functional groups that contain only saturated hydrocarbon chains. For example, NDMA (*N*-nitrosodimethylamine, **Figure 3B**) is the *N*-nitrosamine with both alkyl groups "A" and "B" as methyl, while NDEA (*N*-nitrosodiethyl-amine, **Figure 3B**) is the *N*-nitrosamine with both alkyl groups "A" and "B" as ethyl.



[24] (PRINSTON00074782; ZHP02220191; ZHP02220239.) [Chinese]

[25] (PRINSTON00074782.) [Chinese]

Figure 3. A. General chemical structure of *N*-nitrosamines. **B.** Chemical structures of NDMA and NEDA.

Humans are exposed to nitrosamines such as NDMA and NDEA on a daily basis. These nitrosamines are widely present at low levels in water and food (e.g., dairy products, meat, and vegetables). According to the FDA, "[n]itrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables," and "[e]veryone is exposed to some level of nitrosamines."[26]

Amines are ammonia (NH_3) derivatives in which one or more H (hydrogen) atoms are substituted by an alkyl group (**Figure 4A**). Depending on the number of alkyl substituents on the N-atom, amines can be classified into primary (1^o), secondary (2^o), tertiary (3^o), and quaternary (4^o) amines. As shown in **Figure 4B**, ethylamine is an example of a primary amine, dimethylamine (**5**) is an example of secondary amine, TEA is an example of tertiary amine, and tetraethylammonium chloride is an example of quaternary amine.

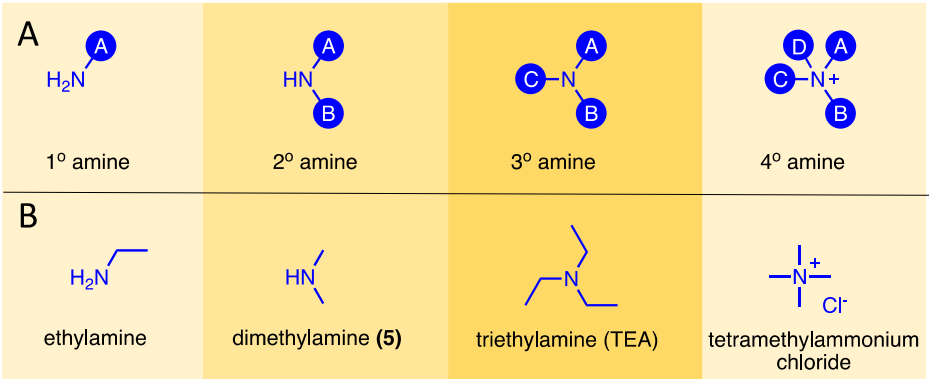


Figure 4. A. General chemical structure of amines. A, B, C, and D represent alkyl groups. **B.** Examples of primary amine propylamine, secondary amine dimethylamine (**5**), tertiary amine TEA, and quaternary amine tetrabutylammonium chloride.

N-Nitrosamines such as NDMA and NDEA can be produced by an organic reaction between an amine and nitrous acid that is formed from sodium nitrite ($NaNO_2$) under acidic conditions. As an example, the mechanism for the formation of NDMA is detailed in **Figure 5**. In an acidic environment such as aqueous HCl, $NaNO_2$ (**1**) reacts with HCl to generate nitrous acid

[26] U.S. FDA, Information about Nitrosamine Impurities in Medications (current as of 11/18/2021) (available at https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications).

(**2**) along with sodium chloride (NaCl). Further reaction of nitrous acid with HCl will produce the protonated nitrous acid (**3**), which then loses a molecule of water (H_2O) to yield the nitrosonium ion (**4,** NO^+). NO^+ is a nitrosating agent that reacts with the nitrogen atom in dimethylamine (**5**) to yield the product NDMA.

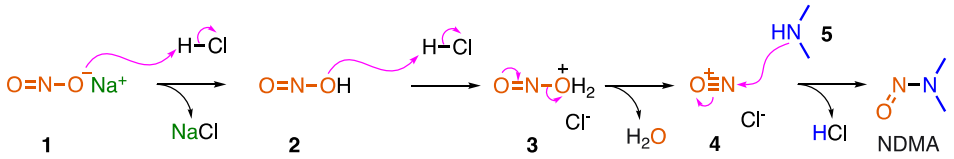


Figure 5. Mechanism for the formation of NDMA from $NaNO_2$ and dimethylamine.

Some nitrosamines can be activated *in vivo* to form a DNA-alkylating agent. Nitrosamines themselves are not causative agents in human cancer. In vivo, nitrosamines must be activated through an a-hydroxylation reaction catalyzed by the cytochrome P450 enzymes (**Figure 6**). For example, when NDMA binds into the active site of P450 enzyme CYP2E1,[27] a hydroxylation reaction takes place at the α-carbon of NDMA (**Figure 6**), to yield the hydroxy compound **6**. Compound **6** eliminates a formaldehyde (HCHO) to produce compound **7**. Protonation of compound **7** generates compound **8**, which undergoes a dehydration reaction (losing a water molecule) to yield alkyldiazonium ion **9**, a DNA alkylating agent. Reaction of methyldiazonium ion **9** with the nucleophilic atoms (such as N atoms on nucleobases of DNA sequences) leads to the formation of a methyl-DNA adduct.

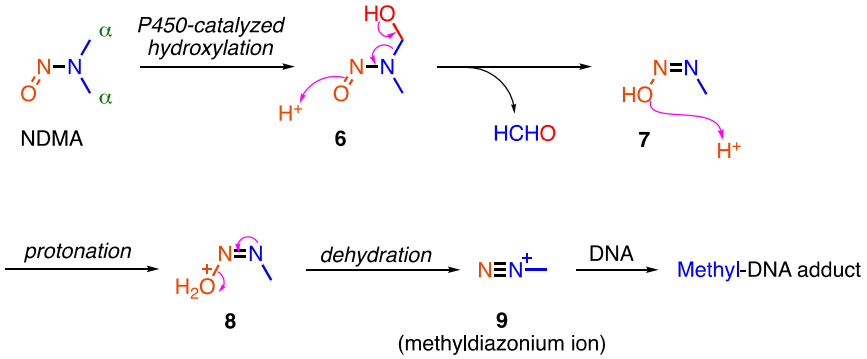


Figure 6. *In vivo* cytochrome P450-mediated activation of NDMA to produce the DNA alkylating methyldiazonium ion (**9**).

[27] Fujita K, Kamataki T. (2001) Role of human cytochrome P450 (CYP) in the metabolic activation of *N*-alkylnitrosamines: application of genetically engineered *Salmonella typhimurium* YG7108 expressing each form of CYP together with human NADPH-cytochrome P450 reductase. *Mutat. Res.*, 483(1-2), 35-41.

The P450-mediated hydroxylation activation is not a universal reaction for nitrosamines. As depicted in **Figure 6**, a nitrosamine leads to the generation of a DNA-alkylating alkyldiazonium ion (such as methyldiazonium ion **9** from NDMA) only when the required P450-catalyzed hydroxylation reaction happens on the α-carbon of the nitrosamine. To achieve a successful hydroxylation reaction at the α-carbon, the nitrosamine (#1, **Figure 7A**) must: (1) have a scaffold that can fit into the active site of the P450 enzyme; and (2) effectively expose its α-carbon (labeled in green, **Figure 7**) to the activated hydroxy group in the active site of the P450 enzyme. On the other hand, a nitrosamine (#2) that cannot fit into the active site of the P450 enzyme (**Figure 7B**) or a nitrosamine (#3) that cannot expose its α-carbon to the enzyme-activated hydroxy group after binding (**Figure 7C**) will not receive a hydroxy group at its α-carbon. As a result, the corresponding DNA-alkylating agent alkyldiazonium ion will not be formed. Overall, it is not reasonable to assume all nitrosamines can lead to a DNA-alkylating agent. As an example, it has been reported that *N*-nitrosoproline (**Figure 7D**) is not metabolized in vivo[28] and is non-mutagenic and non-carcinogenic.[29]

[28] Chu C, and Magee PN (1981) Metabolic fate of nitrosoproline in the rat. Cancer Res., 41, 3653-3657.

[29] IARC (1978) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 17, Some Nitroso Compounds. IARC Scientific Publications, Lyon.

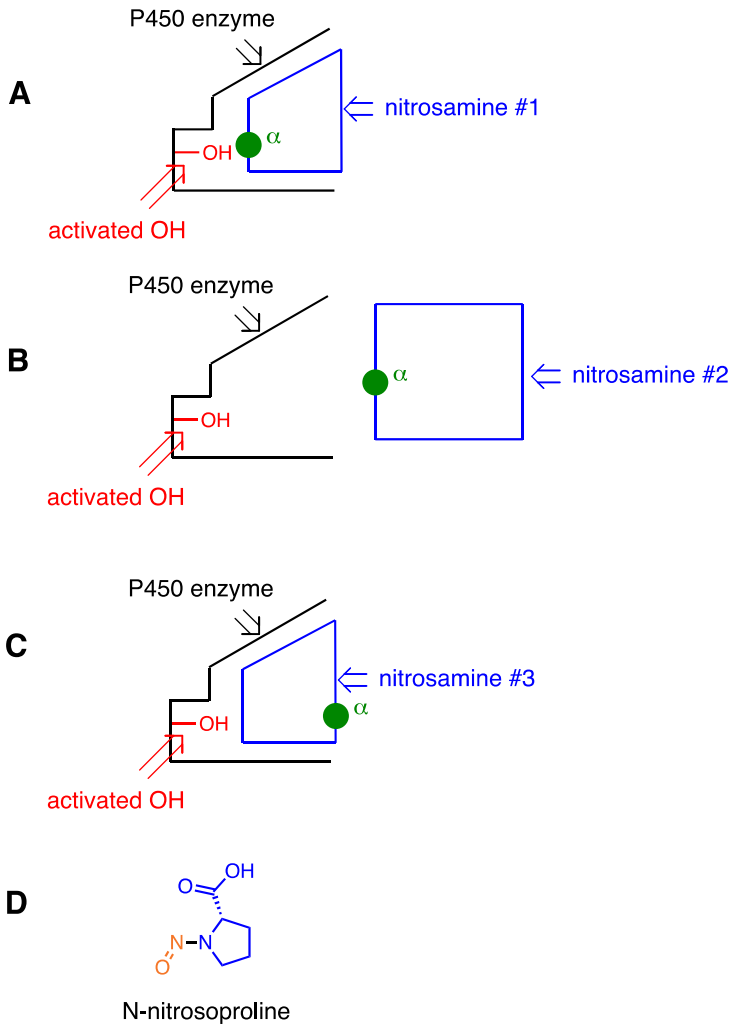


Figure 7. **A**. Binding model of nitrosamine #1 for successful P450 hydroxylation-mediated activation. **B.** Nitrosamine #2 cannot fit into the active site of P450. **C.** Nitrosamine #3, although it can fit into the active site of P450 enzyme, cannot expose its α-carbon in a close proximity to the activated hydroxy (OH) group in the active site of P450. **D.** The chemical structure of N-nitrosoproline.

A. Nitrosamine Formation From Secondary Amines (Dimethylamine)

N-Nitrosamines such as NDMA and NDEA can be produced by an organic reaction between an amine and nitrous acid that is formed from sodium nitrite ($NaNO_2$) under acidic conditions. As an example, the mechanism for the formation of NDMA is detailed in **Figure 5**, above. Although the method of nitrosamine formation from a secondary amine and nitrous acid

(sodium nitrite + inorganic acid) generally has been documented in the literature,[30] in the past several decades, little progress has been made and only a few alternative nitrosating agents have been reported for different reaction environments.

For instance, under acidic conditions (pH <=3), the nitrosating agent can mainly be dinitrogen trioxide (N_2O_3) or nitrosyl halide besides NO^+,[31] while under basic or neutral conditions, effective nitrosating agents include nitroprusside (e.g., sodium nitroprusside)[32] or alkyl nitrites (RO-N=O).[33] Other nitrosating agents, such as nitrogen tetroxide,[34] oxyhyponitrite,[35] Fermy's salt,[36] *N*-haloamides,[37] and oxalic acid[38] have also been reported. Moreover, a small number of heterogeneous systems employing acidic reagents (e.g., Nafion-H,[39] trichloroisocyanuric acid,[40] and tungstate sulfuric acid (TSA)[41]) in combination with $NaNO_2$ have also been used.

I learned of the possibility of a nitrosamine formation reaction from nitrosomium ion (NO^+) and a secondary amine because of the nNOS inhibitor project that I worked on as a postdoc at Northwestern University. Since then, however, I have not encountered any opportunity to teach this reaction in either my undergraduate courses (e.g., Organic Chemistry I and Organic Chemistry II) and or my graduate-level courses (e.g., Organic Synthesis in Drug Design and Medicinal

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30 Datin RC, Elliott GA. (1964) Synthesis of nitrosodimethylamine. US PCT #US3136821A.

31 Williams, D. L. H. Nitrosation Reactions and the Chemistry of Nitric Oxide, 1st ed.; Elsevier Science: Amsterdam, Oxford, 2004.

32 Touster, O. Determination of keto–enol equilibrium constants and the kinetic study of the nitrosation reaction of b-dicarbonyl compounds. In Organic Reactions; Wiley: New York, 1953; vol. 7, chapter 6.

33 Garcia Rio, L.; Leis, J. R.; Iglesias, E. Nitrosation of amines in nonaqueous solvents, 1: Evidence of a stepwise mechanism. J. Org. Chem. 1997, 62, 4701.

34 Makhova, N. N.; Karpov, G. A.; Mikhailyuk, A. N.; Bova, A. E.; Khamel_nitskii, I.; Novikov, S. S. (1978) *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1, 226.

35 Chang, S. K.; Harrington, G. W.; Rothstein, M.; Shergalis, W. A.; Swern, D.; Vohra, S. K. (1979) *Cancer Res.* 39, 3871.

36 Castedo, L.; Riguera, R.; Vezquez, M. P. (1983) *J. Chem. Soc., Chem. Commun.*, 301.

37 Nakajima, M.; Warner, J. C.; Anselme, J. P. (1984) Tetrahedron Lett., 25, 2619.

38 Zolfigol, M. A. (1999) Synth. Commun., 29, 905.

39 Zolfigol, M. A.; Habibi, D.; Mirjalili, B. F.; Bamoniri, A. (2003) Tetrahedron Lett., 44, 3345.

40 Zolfigol, M. A.; Ghorbani-Choghamarani, A.; Hazarkhani, H. (2002) Synlett, 1002.

41 Bahador Karami, Morteza Montazerozohori, and Mohammad Hossein Habibi (2005) Tungstate Sulfuric Acid (TSA) / $NaNO_2$ as a Novel Heterogeneous System for the N-Nitrosation of Secondary Amines under Mild Conditions. Bull. Korean Chem. Soc., 26(7), 1125.

Chemistry). During the past 11 years in my own research lab, I have never used this reaction in any of my projects. In my opinion, nitrosamine formation from nitrous acid and secondary amine is a documented but rather uncommon reaction.

While I recognize that nitrosamines can be formed when treating secondary amine with nitrous acid, I was not aware, prior to my involvement in this case, that a reaction mixture containing nitrile starting material + sodium azide (NaN_3) + zinc chloride ($ZnCl_2$) + DMF would generate a secondary amine. According to plaintiffs' experts, DMF, a commonly-used solvent, can degrade into dimethylamine, which is a secondary amine, and dimethylamine can react with any NO^+ that might be available in the reaction mixture and lead to the formation of NDMA (**Figures 5** & **8**).

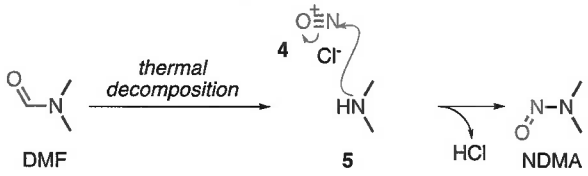

Figure 8. Decomposition of DMF to generate dimethylamine that undergoes nitrosation with NO^+ (**4**) to produce NDMA.

Plaintiffs' experts rely on a textbook for the proposition that it is commonly known that DMF can degrade into dimethylamine.[42] This text merely states that "DMF decomposes slightly at its normal bp [boiling point] (153C) to give small amounts of dimethylamine and CO." In ZHP's $ZnCl_2$ process, however, DMF was used as the solvent in the crude Valsartan (step #4) (*See* **Figure 2**, bottom). For this step, the reaction was done by mixing the starting material with NaN_3 in the presence of $ZnCl_2$ at 135±2 °C for 20±1 hours.[43] Note that the reaction temperature for the $ZnCl_2$ process was significantly lower than the boiling point of DMF (153 °C). The reaction was then cooled to [redacted] °C, and was added to another solvent, MTBE, followed by water. After cooling the mixture to [redacted] °C, $NaNO_2$ was added and the pH value of the mixture was adjusted to pH <=3 using HCl (6N), while maintaining the temperature [redacted] °C.[44]

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42 *See Purification of Laboratory Chemicals*, Armarego, WLF (1996 (Edition 4th), 2009 (Edition 6th)) (cited in 2022 Najafi Rep. at 26; 2022 Hecht Rep. at 5; Bain Rep. at 10).

43 (ZHP025789969.)

44 (*Id.*)

It is also reported in Armarego (1996 (Edition 4th) 2009 (Edition 6th)) that "DMF decomposition is catalyzed by acidic and basic materials, so that even at room temperature, DMF is appreciably decomposed if allowed to stand for several hours with solid KOH, NaOH, CaH_2."[45] However, solid KOH, NaOH, CaH_2 represent strong bases, which create an unusually strong basic environment around the solid base themselves. In my opinion, the reaction condition of the crude Valsartan (step #4) in the $ZnCl_2$ process was neutral and is dramatically different from the strong basic conditions in the presence of solid bases KOH, NaOH, CaH_2. I have not seen evidence that acidic condition would catalyze the decomposition of DMF. During the quenching process of the $ZnCl_2$ process, the pH value was adjusted to <=3.[46] The solvent DMF is generally known to be stable under this weakly acidic condition.

B. Nitrosamine Formation From Tertiary Amines (TEA)

Distinct from secondary amines, reaction of tertiary amine with nitrosonium ion (NO^+) involves a much more complicated mechanism and the overall reaction, therefore, is dramatically slower.[47,48] As an example, formation of NDEA from TEA is detailed in **Figure 9**. TEA must first react with NO^+ (**4,** *see* **Figure 5**, above) to generate a nitroso-compound (**10**). The nitroso-compound (**10**) slowly eliminates a nitroxyl (HNO) molecule,[6,7] to generate the iminium chloride compound (**11**). Addition of a water molecule to the iminium ion (**11**) gives the hydroxylated intermediate (**12**), which then eliminates an acetaldehyde (**13**) to yield diethylamine (**5a**), a secondary amine that is analogous to dimethylamine (**5**, *see* **Figure 5**, above). Similar to dimethylamine **5**, diethylamine **5a** can be nitrosated by NO^+ (**4**) to finally produce the nitrosamine NDEA. Overall, the mechanism of NDEA formation from TEA takes four more steps than that of NDMA formation from dimethylamine.

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45 (Armarego (1996 (Edition 4th)), Page 206.

46 (ZHP02579969.)

47 Smith PAS, Loeppky RN. (1967). Nitrosative cleavage of tertiary amines. *J. Am. Chem. Soc.* 89, 1147-1157.

48 Smith PAS, Pars HG. (1959). Nitrosative cleavage of N',N'-dialkhylhydrazides and tertiary amines. *J. Org. Chem.* 24, 1325-1332.

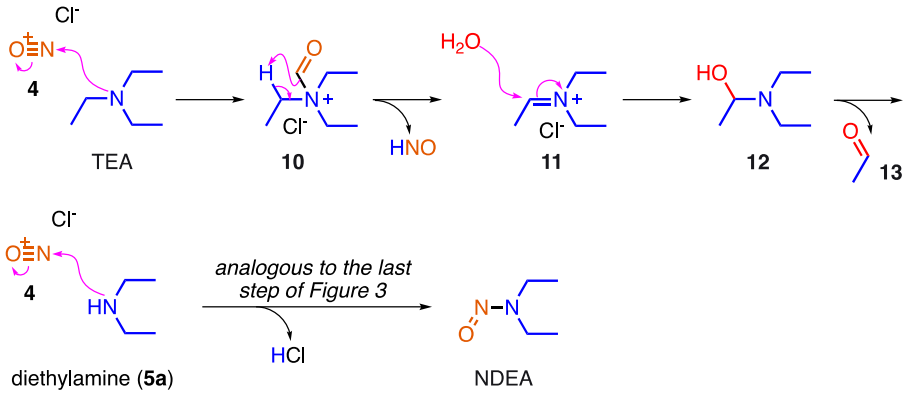

Figure 9. Mechanism for the formation of NDEA from nitrosonium ion (**4,** NO^+) and TEA.

The nitrosation reactions of tertiary amines (e.g., TEA) were far less known than those of secondary amines (e.g., dimethylamine and diethyamine). Historically, there has been argument as to whether tertiary amines react with nitrous acid.[49] A literature search related to the synthetic method to the production of NDEA from TEA on SciFinder[50] only generated 10 known publications. Common reactions are typically reported in tens of thousands of publications. Moreover, none of these journal articles addresses the use of nitrous acid (or sodium nitrite + inorganic acid) and TEA to produce NDEA. Instead, all the published methods included a special nitrosating reagent such as the Fremy's salt,[51] nitric acid/acetic anhydride,[52] N_2O_3,[53] and N_2O_4[54] to facilitate the formation of NDEA. It is worth noting that, at low pH, a tertiary amine (e.g., TEA)

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[49] Hein GE. (1963) the reaction of tertiary amines with nitrous acid. J. Chem. Educ. 40(4):181.

[50] SciFinder is produced by Chemical Abstracts Service (CAS). It is the most comprehensive database for the chemical literature. SciFinder can search by topic, author, substances (by name or CAS Registry Number). In addition, one can also use the editor feature to draw chemical structures, substructures, or reactions. SciFinder is a core research tool for chemistry, chemical engineering, materials science, and other science and engineering disciplines.

[51] Castedo, Luis; et al, (1983) Fremy's salt (potassium nitrosodisulfonate): a nitrosating reagent for amines. 6, 301-302.

[52] Boyer JH, Pillai TP, Ramakrishnan VT. (1985) Nitrosamines and nitramines from tertiary amines. Synthesis, 677-679.

[53] Rosadiuk, Kristopher A.; et al, (2018) Isolable Adducts of Tertiary Amines and Dinitrogen Trioxide. European Journal of Inorganic Chemistry, 41, 4543-4549.

[54] Boyer, Joseph H.; et al, (1985) Nitrosamines from tertiary amines and dinitrogen tetraoxide. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999), (8), 1661-4; Iranpoor, Nasser; Firouzabadi, Habib; Pourali, Ali. (2005), Dinitrogen tetroxide-impregnated charcoal (N2O4/Charcoal). Selective nitrosation of amines, amides, ureas, and thiols. Synthetic Communication, 35(11), 1517-1526.

forms an unreactive ammonium salt due to the protonation of the amino nitrogen atom. As a result, usually no reaction can be detected in cold diluted reaction mixture.

V. ZHP Performed Adequate Risk Assessments For The Various Routes Of Synthesis It Used To Manufacture Valsartan API Given What Was Reasonably Known At The Time Of Manufacture.

As set forth above, ZHP utilized several different processes to manufacture its Valsartan API from 2007 to 2018.[55] ZHP filed Drug Master File amendments with the FDA documenting each of those manufacturing processes that included assessments of the risks of the process and results of chromatography testing documenting impurities resulting from the process.[56] Based on my review of plaintiffs' experts' reports, none of plaintiffs' experts has identified any concerns raised by the FDA in response to these Drug Master File amendments or any subsequent filings with the FDA regarding Valsartan medications that incorporate the Drug Master File.

Plaintiffs' experts, including, but not limited to, Drs. Hecht and Najafi, assert that ZHP's risk assessments for the TEA process with quenching[57] and $ZnCl_2$ process[58] were inadequate because ZHP failed to specifically investigate whether either of these processes was capable of resulting in the formation of nitrosamines.[59] But the experts' opinions are based on present-day scientific knowledge regarding complex chemistry processes that can result in nitrosamine formation – not what was reasonable or expected a decade ago. Chemistry is an evolving science that is constantly changing as new technologies and testing develop over time. As an example, the Huisgen cycloaddition reaction was first introduced by Rolf Huisgen in 1960.[60] However, in the

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55 (PRINSTON00000008-PRINSTON00000009.)

56 (*See* PRINSTON00000027 (noting the submission of Process I (DMF No. 020939) to the FDA); PRINSTON00000008; ZHP01458188 (submission of Process II (DMF No. 023491) to the FDA); PRINSTON00079747-PRINSTON00079755 (submission of Amendment-002 to DMF No. 023491, which added quenching to the TEA Process); PRINSTON00000009; PRINSTON00073120; PRINSTON00073102-PRINSTON00073119 (submission of Amendment-004 to DMF No. 023491, which replaced TEA with $ZnCl_2$).)

57 (PRINSTON00079747.)

58 (PRINSTON00073102.)

59 (*See* 2022 Hecht Rep.at 2 ("ZHP was not looking for NDMA or NDEA because they failed to perform a straightforward assessment of the chemistry."); 2022 Najafi Rep. at 26 ("HNO_2 is plentiful in [$ZnCl_2$ Process Step 4] reaction and the manufacturer did not heed the obvious risk of nitrosamine formation.").)

60 Breugst M, Reissig H-U. (2020). The Huisgen reaction: Milestones of the 1,3-dipolar cycloaddition. Angew. Chem. Int. Ed. 59, 12293.

next 40 years after its discovery, this reaction was not known among life scientists until Barry Sharpless described the potential application of this old reaction in modification and labeling of specific biomolecules in 2001. Since then, tremendous success has been achieved around this reaction, which has been highlighted by the Award of the 2022 Nobel Prize in Chemistry. It is not possible for any chemist to detect all possible impurities that may ever be found to result from a chemical process at some point in the future. Instead, chemistry researchers assess chemical processes for potential impurities that are reasonably expected or suspected to occur based on the scientific knowledge available at the time of inquiry. Similarly, organic process chemists in the pharmaceutical industry responsible for developing drugs and drug manufacturing processes must assess the route of synthesis for the potential formation of impurities that can be reasonably expected or suspected based on the scientific literature and knowledge reasonably available at the time.

At the time ZHP was developing and using the $ZnCl_2$ process and the TEA process with quenching, it was not common knowledge among general chemists or the chemistry community that either of these processes could result in the formation of nitrosamines such as NDMA or NDEA during either the reaction or the quenching procedure. As a result, ZHP conducted a proper evaluation of the $ZnCl_2$ process and the TEA process with quenching based on the scientific knowledge available.

A. ZHP Performed An Appropriate And Reasonable Risk Assessment For The $ZnCl_2$ Process.

A review of company documents and regulatory filings makes clear that ZHP properly conducted a lengthy, multi-phase investigation of the risks of the $ZnCl_2$ process before it was used to manufacture Valsartan API. Plaintiffs' experts are incorrect that this entire investigation was deficient because ZHP did not specifically investigate the possibility of NDMA formation. As set forth below, the formation of NDMA is the result of a multi-step chemical process. With respect to the $ZnCl_2$ manufacturing process, the NDMA formation first requires the degradation of the DMF solvent used in the $ZnCl_2$ process into dimethylamine (**5**, *see* **Figure 5**, above), which then reacts with NO^+ (**4**, *see* **Figure 5**, above) generated from nitrous acid (*see* **Figure 5**, above). But plaintiffs' experts have presented no evidence that such DMF degradation – which plaintiffs' experts assert had been documented at the boiling point of DMF – was expected or even possible at the lower temperatures (135 ^oC) used for the $ZnCl_2$ process.

1. ZHP Properly Conducted A Multi-Step Risk Analysis For The $ZnCl_2$ Process.

Beginning on November 27, 2011, ZHP conducted a self-evaluation and assessment by the ZHP Change Initiate Department.[61] First, the technical department requested the process change for the Valsartan $ZnCl_2$ process (change control # PCRC-11025).[62] The assessment included: (1) process changes content evaluation; (2) suitability of specifications and analytical methods of intermediates and final substance evaluation; (3) manufacturing equipment evaluation; (4) assessment via lab-scale process research and development studies; and (5) quality risk assessment.[63] Specifically, the assessment compared use and quantity change of raw materials, synthetic routes, process description and critical process parameters between the processes.[64]

i. **Raw Material Evaluation Before And After Change.** During the process change, changes were only made in the materials used for acylation and crude product steps (**Table 1a-1** below from ZHP).[65] Specifically, in the acylation step, the acid binding agent was changed from potassium carbonate (K_2CO_3) to the mixture of sodium carbonate (Na_2CO_3) and sodium hydroxide (NaOH).[66] In the tetrazole forming reaction, DMF was used as the solvent to replace toluene and $ZnCl_2$ was used as the catalyst to replace TEA•HCl. In the quenching process, MTBE was added as a solvent.[67]

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61 (ZHP02579962.)

62 (*Id.*)

63 (*Id.*)

64 (ZHP02579962-ZHP02579965.)

65 (ZHP02579963.)

66 (ZHP02579965.)

67 (ZHP02579967.)

Table 1a-1. Raw Materials Comparison before and after Change

Step	Materials before Changes	Materials after Changes	Changes Description
Acylation	Condensation compound hydrochloride	Condensation compound hydrochloride	No change in materials
	Valeryl chloride	Valeryl chloride	
	Process water	Process water	
	Toluene	Toluene	
	Saturated NaCl solution	Saturated NaCl solution	
	Sodium bicarbonate	Sodium bicarbonate	
	Potassium carbonate	Sodium carbonate	Acylation reaction alkali system: replace potassium carbonate with sodium carbonate and sodium hydroxide
		Sodium hydroxide	
	—	DMF	
Crude product	Pentacylated compound toluene solution	Pentacylated compound DMF solution	Tetrazole formation system: $ZnCl_2$, sodium azide and DMF are used instead of triethylamince hydrochloride, sodium azide and toluene. $ZnCl_2$ and DMF are the new materials.
	Triethylamince Hydrochloride	Zinc chloride ($ZnCl_2$)	
	Sodium azide	Sodium azide	
	Toluene	DMF	
	—	MTBE	New solvent used for extraction in quenching and saponification
	—	Toluene	Rinsing solvent
	Sodium hydroxide	Sodium hydroxide	No change
	HCl solution	HCl solution	
	Process water	Process water	
	Ethyl acetate	Ethyl acetate	
	Saturated NaCl solution	Saturated NaCl solution	
	Sodium nitrite	Sodium nitrite	
	Anhydrous magnesium sulfate	Anhydrous magnesium sulfate	

ii. **Main Material Charging Evaluation Before And After Change.** No change was made in the quantities of main materials (**Table 1a-2** below from ZHP).[68]

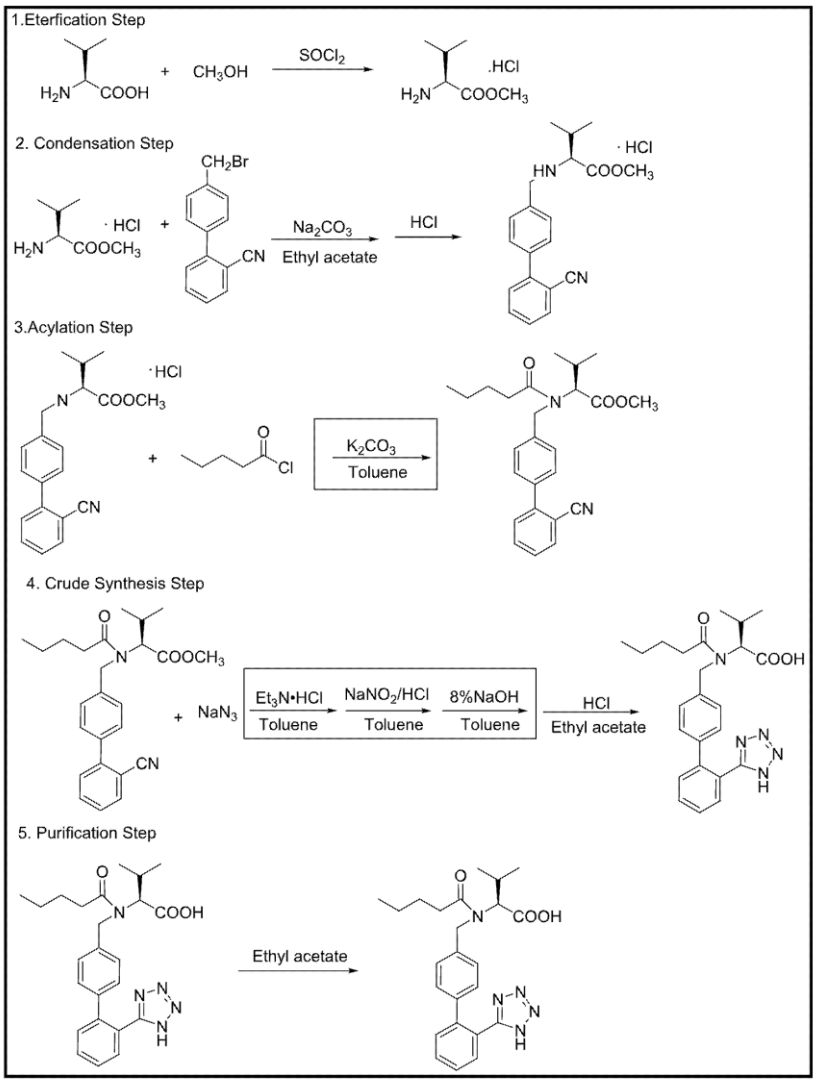
[68] (ZHP02579964-ZHP02579965.)

Table 1a-2. Main Materials Charging and Production Capacity Comparison

Step	Before Changes		After Changes		Changes Description
	Materials Name	Quantity Charged	Materials Name	Quantity Charged	
Esterification	L-Valine	360 kg	[redacted]		
	$SOCl_2$	455 kg			
	Methanol	2150 L			
Condensation	Br-OTBN	320 kg			
	L-Valine methyl ester hydrochloride solution	600-700L			
	Sodium carbonate	300 kg			
	Ethyl acetate	3200 L			
	Saturated NaCl solution	200 L			
Acylation	Condensation compound hydrochloride	435 kg			
	Valeryl chloride	195 kg			
	Toluene	3000 L			
	Potassium carbonate	600 kg			
	——	——			
	——	——			
Crude product	Pentacylated compound toluene solution	1000-1200 L			

Step	Before Changes		After Changes		Changes Description
	Materials Name	Quantity Charged	Materials Name	Quantity Charged	
	Triethylamine Hydrochloride	300 kg	[redacted]		
	Sodium azide	112.5 kg			
	——	——			
	8% Sodium hydroxide	2100 L			
	Sodium nitrite	100 kg			
	HCl solution	600 L			
	Ethyl acetate	4150 L			
Purification	Crude Valsartan	425 kg			
	Ethyl acetate	3150 L			

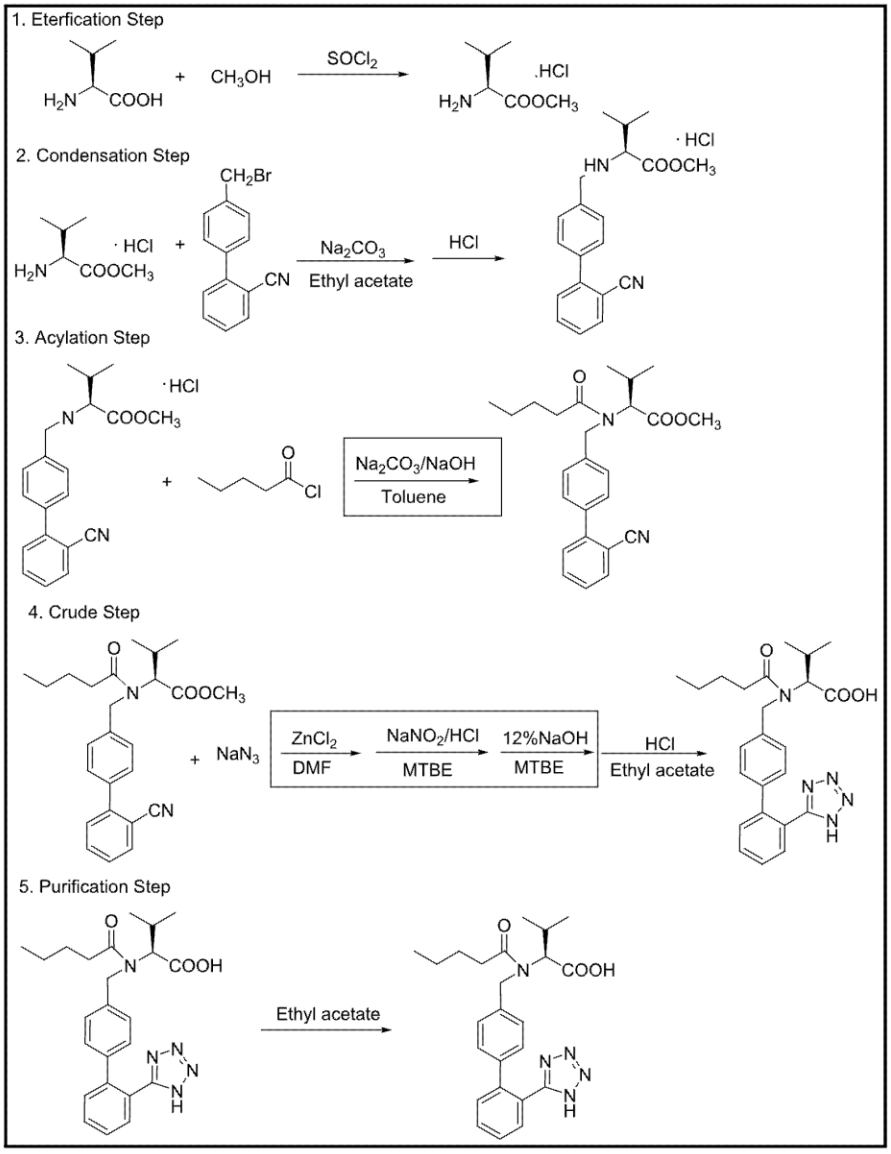
iii. **Synthetic Route And Process Comparison Before And After Change.** In the tetrazole forming reaction, DMF was used as the solvent to replace toluene, and $ZnCl_2$ was used as the catalyst to replace TEA• HCl, as shown in **Figure 1a-2**, **Figure 1a-3**, and **Table 1a-3** below from ZHP.[69]



Note: The process framed above is the changed content.

Figure 1a-2. Synthetic Route of Original Process (Triethylamine Process)

[69] (ZHP02579966-ZHP02579969.)



Note: The process framed above is the changed content.

Figure 1a-3. Synthetic Route of Changed Process ($ZnCl_2$ Process)

Table 1a-3. Description of Main Manufacturing Process Changes

Step	Original Process	Proposed Process	Note on Changes
Valine methyl ester	When reaction is finished under refluxing, cool the batch to 40 – 45°C, then control temperature at 30 - 75°C and vacuum at less than -0.06MPa, distill methanol to dry.	[redacted]	
Condensation compound hydrochloride	When condensation reaction is finished, cool the batch to 30±10°C, settled for 30±5 minutes to obtain separation from the aqueous phase, organic phase is washed with 320±20L of water, 200±20L of unsaturated salt solution (prepared by saturated salt solution) and 320±20L of process water successively.		
Pentanoyl compound	Pump into 1200±50L of process water, charge 600±5kg of potassium carbonate, and stir to dissolve completely, the charge 435kg of condensation compound hydrochloride and 2400±100L of toluene.		
	Control the temperature at 25±5°C, add the Valeryl chloride and toluene mixture solution gradually in 3±1 hours, then the batch is stirred for 2±0.5 hours additionally at this temperature.		
	When acylation is finished, settled for 30±5minutes to delamination. Organic phase is washed with 400±50L of sodium bicarbonate solution (prepared by 400±50L of process water and 32±2kg of sodium bicarbonate) and 1800±100L of process water successively, stir for 30±5 minutes and settled		

Step	Original Process	Proposed Process	Note on Changes
	for 30±5minutes to delamination. Then washed with 600±50L of saturated salt solution, stir for 30±5 minutes and settled for 30±5minutes to delamination.	[redacted]	
Crude Valsartan	**Tetrazole Reaction**: After part of toluene is distilled off, the residual 100 – 2000L of Pentanoyl compound toluene solution is pumped into tetrazole reactor, then add 112.5kg of sodium azide and 300kg of triethylamine hydrochloride, heat to 93-95°C to react for 20±1hours.		
	Quenching operation: Cool the batch to 35±10°C. Pump 300±30L of toluene into tetrazole reactor, stir for 30 minutes. Add 600±40L of process water, stir for 30 minutes, transfer the batch to saponification reactor, wash tetrazole reactor with 100±10L of process water. Add 100±5kg of sodium nitrite, stir for dissolve completely, and adjust pH ≤3 with 500±40L of 6N hydrochloric acid below 10°C.		
	Saponification operation: Add 2100±50L of pre-prepared 8% Sodium hydroxide solution into toluene organic phase, control temperature at 35±2°C, stir and react for 5±0.5 hours. Settled to delamination, pump aqueous layer to acidification reactor.		
Recrystallization	Final crystallization temperature is -5±5°C, and crystallization time is 2±0.5hours		

iv. **Critical Process Parameters Comparison Evaluation.** To reduce the racemization of the product in the saponification reaction, the temperature for this step was changed from 35±2 °C to [redacted]°C. Also, in order to maintain stable production, the critical process parameters were redefined and confirmed as shown in the following **Table 1a-4** from ZHP.[70]

Table 1a-4. Change on Critical Process Parameters

Critical Process Parameters	Original Process	Changed Process	Note on Changes
Reaction time of esterification	5±0.5 hours	[redacted]	
Reaction time of condensation	5±1.0 hours		
Reaction time of acylation	25±5°C		
Reaction time of saponification	35±2°C		
pH for acidification	pH=1.0-2.0		

v. **Evaluation On Suitability Of Specifications And Analytical Procedures Of Intermediates And Final Substance.** The specification of intermediates did not change. Except for the addition of tests related to the new solvents used in the manufacturing process, DMF and MTBE, no change was made to the testing done prior to releasing specification of the final substance. The chemical structures of intermediates were not changed, and the impurity profile of the intermediates remained the same.[71] The specification of the final drug substance for US DMF and EU DMF was changed, and the new tests of DMF and MTBE were added in the releasing test, as detailed in following **Table 1a-5, Table 1a-6,** and **Table 1a-7** from ZHP.[72]

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70 (ZHP02579970.)

71 (ZHP02579971-ZHP02579972.)

72 (ZHP02579971-ZHP02579972.)

Table 1a-5. Comparison on Specification of Condensation Compound Hydrochloride (Intermediate 2)

Test Item	Original Specification
Appearance	White or off-white solid
Identification (IR)	The IR spectrum corresponds to that of RS.
Specific optical rotation	+17.0-+21.5°
Loss on drying	≤3.0%
Related substance OTBN Ethyl-condensation Any other single impurity Total impurities	 ≤1.5% ≤1.0% ≤0.5% ≤2.0%
Purity	≥98.0%

Table 1a-6. Comparison on Specification of Crude Valsartan (Intermediate 4)

Test Items	Original Specification
Appearance	White to light yellow powder
Assay	For information
D-Valsartan	≤5.0%
Related substances (HPLC) Impurity B Impurity C RRT 1.7 impurity Any other single impurity Total impurities	 ≤0.25% ≤0.5% ≤1.0% ≤0.5% ≤2.0%
Purity (HPLC)	≥98.0%

Table 1a-7. Comparison on Specification of Valsartan (US Specification)

Test Items (US)	Original Specification	Proposed Specification	Note
Appearance	White or off-white powder. Odorless, slightly hygroscopy.	White or off-white powder. Odorless, slightly hygroscopy.	No change
Solubility	Freely soluble in methanol, particularly insoluble in water.	Freely soluble in methanol, particularly insoluble in water.	No change
Identification A	Infrared absorption spectrum corresponds to the spectrum obtained with the RS.	Infrared absorption spectrum corresponds to the spectrum obtained with the RS.	No change
Identification B	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay.	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay.	No change
Absorbance	≤0.02	≤0.02	No change
Water	≤2.0%	≤2.0%	No change
Residue on ignition	≤0.1%	≤0.1%	No change
Heavy metals	≤0.001%	≤0.001%	No change
D-Valsartan	≤1.0%	≤1.0%	No change
Related substances Impurity B Impurity C Any other single impurity Total impurities	 ≤0.2% ≤0.10% ≤0.10% ≤0.30%	 ≤0.2% ≤0.10% ≤0.10% ≤0.30%	No change
Assay (HPLC)	98.0-102.0%	98.0-102.0%	No change
Residual solvents 1 (GC) Ethanol Ethyl acetate Toluene	 ≤5000 ppm ≤5000 ppm ≤890ppm	 ≤5000 ppm ≤5000 ppm ≤890ppm	The solvents of DMF and MTBE are new added in $ZnCl_2$ process, and both of them are added in the specification of residual solvents
Residual solvents 2 (GC) DMF MTBE	 — —	 ≤880 ppm ≤5000 ppm	

vi. **Manufacturing Facility And Equipment Evaluation.** Because the quantities of main materials and the batch size were not changed, the previous equipment was used for production, as detailed in the following table from **Table 1a-8** from ZHP.[73]

Table 1a-8. Comparison on Main Equipments

Process	Step	Original process equipment			Changed process equipment			Note
		No.	Size	Material	No.	Size	Material	
Step 1	Esterification	Reactor II-101	3000 L	Glass -lined	Reactor II-101	3000 L	Glass -lined	No change
	Concentration	Reactor II-105	3000 L	Glass -lined	Reactor II-105	3000 L	Glass -lined	No change
Step 2	Concentration	Reactor II-201	6000 L	Glass -lined	Reactor II-201	6000 L	Glass -lined	No change
		Reactor II-211	6000 L	Glass -lined	Reactor II-211	6000 L	Glass -lined	No change
	Filteration	Centrifuge II-203	1250	Plastic -lined	Centrifuge II-203	1250	Plastic -lined	No change
	Drying	Dryer II-704	3000 L	Glass -lined	Dryer II-704	3000 L	Glass -lined	No change
		Dryer II-705	3000 L	Glass -lined	Dryer II-705	3000 L	Glass -lined	No change
Step 3	Acylation	Reactor II-218	5000 L	Stainless steel	Reactor II-218	5000 L	Stainless steel	No change
		Reactor II-218	5000 L	Stainless steel	Reactor II-218	5000 L	Stainless steel	No change
Step 4	Tetrazole Reaction	Reactor II-231	3000 L	Glass -lined	Reactor II-231	3000 L	Glass -lined	No change
		Reactor II-239	3000 L	Glass -lined	Reactor II-239	3000 L	Glass -lined	No change
	Quenching/ Saponification	Reactor II-241	5000 L	Glass -lined	Reactor II-241	5000 L	Glass -lined	No change
		Reactor II-247	5000 L	Glass -lined	Reactor II-247	5000 L	Glass -lined	No change
	Acidification	Reactor II-250	6000 L	Glass -lined	Reactor II-250	6000 L	Glass -lined	No change
		Reactor II-255	6000 L	Glass -lined	Reactor II-255	6000 L	Glass -lined	No change
	Condensation/ Crystallization	Reactor II-262	5000 L	Glass -lined	Reactor II-262	5000 L	Glass -lined	No change
		Reactor II-267	5000 L	Glass -lined	Reactor II-267	5000 L	Glass -lined	No change
	Centrifugation	Centrifuge II-275	SS1250	Stainless steel	Centrifuge II-275	SS1250	Stainless steel	No change

[73] (ZHP02579973-ZHP02579974.)

Process	Step	Original process equipment			Changed process equipment			Note
		No.	Size	Material	No.	Size	Material	
		Centrifuge II-276	SS1250	Stainless steel	Centrifuge II-276	SS1250	Stainless steel	No change
Step 5	Dissolving	Reactor II-401	5000 L	Stainless steel	Reactor II-401	5000 L	Stainless steel	No change
	Filtration	Filter II-402	Φ800× 600	Stainless steel	Filter II-402	Φ800× 600	Stainless steel	No change
	Crystallization	Reactor J08-101	4000 L	Stainless steel	Reactor J08-101	4000 L	Stainless steel	No change
	Transfer	Reactor J08-103	4500 L	Stainless steel	Reactor J08-103	4500 L	Stainless steel	No change
	Centrifugation	Centrifuge J08-102	SS1250	Stainless steel	Centrifuge J08-102	SS1250	Stainless steel	No change
		Centrifuge J08-104	SS1250	Stainless steel	Centrifuge J08-104	SS1250	Stainless steel	No change
	Drying	Dryer J08-107	3000 L	Stainless steel	Dryer J08-107	3000 L	Stainless steel	No change
		Dryer J08-108	3000 L	Stainless steel	Dryer J08-108	3000 L	Stainless steel	No change
	Milling	Pulverizer J08-109	FZ-450	Stainless steel	Pulverizer J08-109	FZ-450	Stainless steel	No change
	Mixing	Mixer J08-110	2000 L	Stainless steel	Mixer J08-110	2000 L	Stainless steel	No change

vii. **Assessment In Lab-Scale Research And Development Study.** The lab-scale process research and development for the changes in crude Valsartan (step #4), including solvent selection and catalyst selection for the tetrazole forming reaction, and the experiment design for saponification temperature were evaluated, as detailed in the following **Figures 1a-4** to **1a-6** from ZHP.[74]

[74] (ZHP02579977-ZHP02579978.)

English Translation for Figure 1a-4 to Figure 1a-6

5.4. Crude Valsartan Step

5.4.1 Existing Problem in Original Process

Based on the current analysis results and the triethylamine process production actual situation, the main problems existed in the original process are as following:

1) The **conversion rate** of tetrazole formation to crude product is relatively low at about 55-70% and around 30% of pentacylated compound (intermediate) cannot be totally reacted with not high yield. It results in comparably high material consumption and cost, so as to further aggravate the post-processing of waste.

2) The quenching procedure for the residual azide uses toluene as solvent, it appears slight emulsification during the quenching and separation operation, the layers interface is too blurred to separate easily.

3) In saponification of this step it easily shows racemization which would cause the relatively high level of D-Valsartan (enantiomer) and impact the product quality.

5.4.2 Development of Proposed Process and Improvement[1]

(1) It develops the new system for tetrazole formation, which applies zinc chloride ($ZnCl_2$), sodium azide, dimethylformamide (DMF) to alternatively replace the original triethylamine hydrochloride (TEA), sodium azide, and toluene. The **conversion rate** is elevated to over 90% and reduces the residual intermediate pentacylated compound. The detailed study results are in the table below:

Table 5-1 Optimization Experiments Result for Tetrazole Formation

R&D Batch No.	Process Conditions	Conversion of Intermediate 3	Note
SC-1141-A-415-032	Pentacylated compound : Sodium azide : TEA = 1 : 1.9 : 2.2; Toluene as solvent, 90~95°C, 20 hours.	58.3%	Original process
SC-1141-GY-011-028	Pentacylated compound : Sodium azide : $ZnCl_2$ = [redacted] DMF as solvent, 130~135°C, 20 hours.	94.9%	After change

From the above results, the new process greatly increases the raw materials conversion, the reaction effect is quite good.

In the scaling up process for the lab research, the residual toluene from intermediate pentacylated compound may widely impact the subsequent tetrazole formation. It will result in reaction speed decline, and raw materials conversion reduction. Considering the tetrazole formation use DMF as solvent with high boiling point, it can apply drag

[1] (a) Gallante, R. J. U.S. Patent 5,502.191, 1995. (b) Tokuhara, G.; Yamaguchi, T.; Iwasaki, T. WO Patent 1996-37481, 1996.

distillation with DMF to remove toluene in pentacylated compound completely [redacted] in lab research can readily resolve the residual toluene issue and ensure the subsequent tetrazole formation in normal reaction. Detailed results are showed in the table below:

Table 5-2 Experiments Result for Drag Effect to Tetrazole Formation

R&D Batch No.	Process Conditions	Conversion of Intermediate 3	Note
SC-1141-406-065	Raw material condensation compound is charged from 2.5 g scaled-up to 50 g, no drag by DMF after acylation.	① 83.74% for 20 hours ② 94.02% for 40 hours	Original process
SC-1141-406-066	[redacted]	99.02% for 20 hours	After change

[redacted]

viii. **Quality Risk Evaluation On Impurities.** The evaluations were performed on the condensation product hydrochloride (**Table 1a-9**, below),[75] crude Valsartan (**Table 1a-10**, below),[76] and final drug API (**Figure 1a-7**, below).[77]

[75] (ZHP02579979-ZHP02579980.)

[76] (ZHP02579981-ZHP02579983.)

[77] (ZHP02579985.)

Table 1a-9. Impurity Evaluation of Condensation Compound Hydrochloride

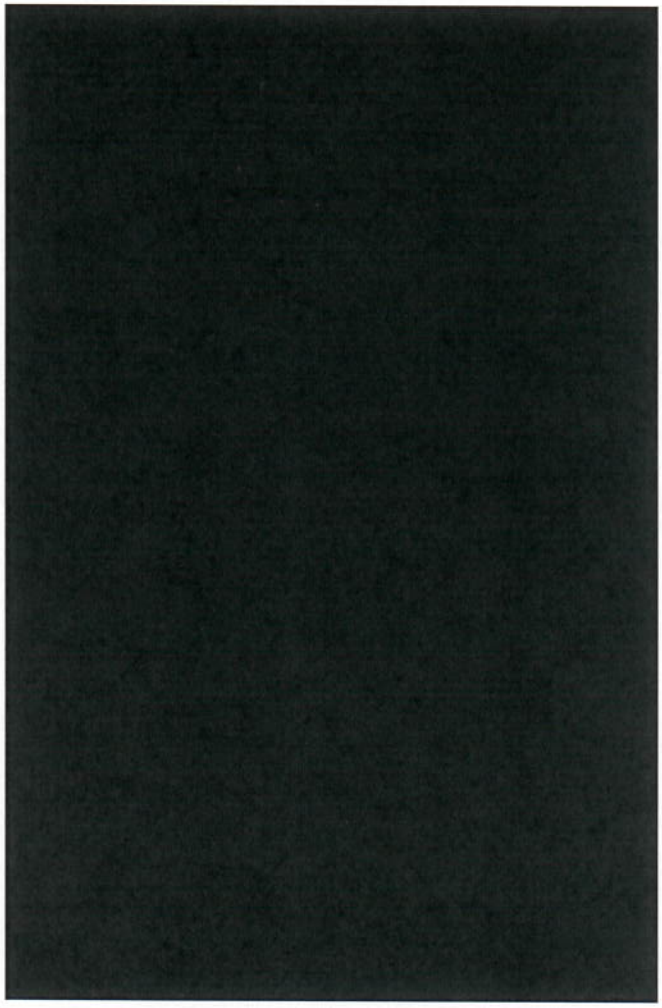

Table 1a-10. Impurity Evaluation of Crude Valsartan

English Translation for Figure 1a-7

(3) Evaluation of drug substance

Change in drug substance process: slightly increase the final temperature of crystallization. This change has no influence on quantity of impurity, while improve the quality of drug substance.

7.2.1.3 Measures should to be taken

Process changes have influence on quantity of impurity including the newly introduced materials sodium carbonate, zinc chloride, DMF and methyl tert butyl ether. They should be evaluated the residual quantity in drug substance. It should pay attention to ignition residue, zinc residue and organic solvents residue. Newly introduced impurity has mature detection methods which has small quality risk.

Process changes may have an impact on produced quantity of some impurities, It is necessary to compare the levels of impurities after change.

7.2.2 Assessment of Polymorphism

7.2.2.1 Description of Polymorphism

Sixteen polymorphic forms for Valsartan drug substance have been reported. The polymorphism of Huahai's Valsartan is amorphous form. No other polymorphic forms were found in the current crystallization process.

7.2.2.2 Risk Assessment of Polymorphism

In the recrystallization step of Valsartan, the change was only made in the final crystallization temperature. Generally, this change won't have effect on the polymorphism of the final drug substance. Therefore, the risk of the change is low.

7.2.3 Assessment of Other Quality Attributes

The changes are mainly made in the crude Valsartan step. There are still three steps away from the final substance, including the hydrolysis reaction, the purification step and the packaging step. Therefore, there is low impact of the changes to the quality attributes, and only the comparison of the quality for the product needs to do during the new process validation.

In addition, ZHP conducted a change committee assessment and QA final approval.[78] The process change for Valsartan $ZnCl_2$ process (PCRC-11025) was proposed by the technical department and evaluated.[79] The process change was then submitted to a change control committee (consisting of a technical department, production department, QC department, EHS department, engineering department, regulatory affairs department and QA department) to conduct the change risk review. The change control committee supplemented a risk assessment of the Valsartan process change request (PCRC-11025) as detailed in the following **Table 1a-11** from ZHP.[80]

78 (ZHP02579986.)

79 (ZHP02579986.)

80 (ZHP02579986.)

Table 1a-11. Risk Assessment from Change Control Committee

Dept.	Evaluation Results	Responsible Department	Date
Technical department	Agree with the proposed change, need to perform the process validation, revise the process procedure and batch record, and perform stability study.	Yang K.	2011.11.27
Production department	Agree with the proposed change, revise the station operation SOP.	Wang X. J.	2011.11.27
QC	Need to additional test residue of $ZnCl_2$, and residual solvents used the manufacturing process, and complete the method validation.	Li Q. M.	2011.11.27
EHS	The wastewater has undergone desalination pretreatment and has no effect on wastewater treatment, agree with the proposed change.	Sheng G. S.	2011.11.27
Engineering department	Existing equipment can meet the requirements of changed process without equipment qualification.	Lu Y. L.	2011.11.27
RA	Provides a comparison with Process II (CEP process), and notifies the customers and Authority based on the comparison result. The proposed change is classified as a critical change, thus a CEP major change will be applied, and the proposed changes will only be implemented after approved by Authority.	Liu Y. F.	2011.11.29
QA	Agree with the proposed change. 1. Technical department prepare process validation protocol, and organize process validation. 2. Technical department prepare process procedure, operation SOPs, batch records, and train on personnel. 3. QC conducts method validation for additional testing, prepare analytical procedures and train on personnel. 4. QC conducts stability study on the process validation batches, and prepares stability protocol. QC prepares additional specification limits and analytical procedures for the testing of residue Zinc and residual solvents. 5. RA updates DMF and notifies customers and authorities. 6. QA follow-up.	Hu Y. L.	2011.11.29

After the change control committee passed the evaluation of the Valsartan process change request (PCRC-11025), it was approved by QA, and five action items were established, as shown in the following **Table 1a-13** from ZHP.[81]

[81] (ZHP02579987.)

Table 1a-13. Action Items established for the $ZnCl_2$ Process Change Control

No.	Action Description	Responsible Department	Responsible Person	Planned Schedule
1	Confirm that all equipments in the workshop have been validated.	Engineering department	Lu Y. L.	2011.12
2	The technician drafts the protocol for process validation, and completes the training of relevant staff, collects the process control data, completes the process validation report, compiles the process procedure, the station operation procedure and the batch record, and completes the training of the staff.	Technical department	Zhou X. H.	2012.4
3	QC completes the validation of the analytical method, performs the testing work in the validation process, formulates the protocol of stability study, conduct the stability test for the validation batches.	QC	Li Q. M.	2012.4
4	Organize Staffs from workshop 2 to manufacture according to the process validation protocol.	Workshop 2	Wang X. J.	2012.4
5	RA updates the DMFs and informs the authorities and clients.	RA	Zhou T.	2013.12

Overall, ZHP conducted a comprehensive and complete risk assessment for Change Request PCRC-11025 to study the potential impact of proposed changes on the quality of the intermediates or the final API for this process change.

It is clear from the records documenting ZHP's multi-step assessment of the $ZnCl_2$ process that the goal of this change was to improve the manufacturing process for Valsartan API. Specifically, ZHP sought to improve the conversion of the tetrazole formation in the crude Valsartan (step #4). According to ZHP records ("**Table 5-6**. Optimization Experiments Result for Tetrazole Formation"), the conversion of intermediate 3 (the *CN*-starting material of the tetrazole formation reaction) was improved from 58.3% in the TEA process to 94.9% in the $ZnCl_2$ process.[82] ZHP performed quality risk evaluation on impurities for all the steps before and after the change from the TEA process to the $ZnCl_2$ process.[83] For each of the steps, the evaluation was conducted with regard to organic/inorganic impurities (including intermediates, by-products, and starting raw material) and solvents (including toluene, DMF, MTBE, and ethyl acetate). In particular, the residual quantity of new material $ZnCl_2$, new solvent DMF, and MTBE were carefully followed during the reaction.

82 (ZHP00245062.)

83 (ZHP00245064.)

ZHP's risk assessment procedure for the $ZnCl_2$ process change was conducted in a formal and comprehensive way that sufficiently evaluated the potential impact of the proposed changes on the quality of the API Valsartan.

2. ZHP Did Not Have Reason To Investigate The Possibility Of NDMA Formation As Part Of Its $ZnCl_2$ Process Risk Assessment.

Plaintiffs' experts opine that ZHP should have known that NDMA formation was a possible result of the $ZnCl_2$ manufacturing process, and therefore a proper risk assessment would have specifically investigated whether any of the trace-level impurities in Valsartan API, which FDA regulations did not require it to identify, were NDMA.[84]

According to plaintiffs' experts, ZHP should have known that the use of DMF as a solvent in the $ZnCl_2$ process created a risk of nitrosamine formation because DMF can degrade into dimethylamine, which can react with nitrous acid to create N-nitroso compounds.[85] But neither of these steps was reasonably foreseeable at the time the $ZnCl_2$ process was assessed and used.

First, as set forth in detail above, NDMA formation requires the presence of a secondary amine along with NO^+ (**4**) generated from nitrous acid (or sodium nitrite + inorganic acid). (*See* **Figure 5**, above.) DMF is one of the common organic solvents that have been used in organic synthesis.[86] DMF is not a secondary amine and cannot react with nitrous acid to result in an *N*-nitroso compound. Instead, DMF is a solvent that was used in the crude Valsartan (step #4) of the reaction. For this step, the reaction was done by mixing the starting material with NaN_3 in the presence of $ZnCl_2$ at 135±2 °C for 20±1 hours.[87] The reaction was then cooled to [redacted] °C, another, another solvent (MTBE) was added, followed by water. After cooling the mixture to [redacted] °C,

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[84] (*See, e.g.*, 2022 Najafi Rep.. at 28 ("ZHP's risk assessment should have led them to monitor formation of multiple potential nitrosamines including NDMA and NDEA."); 2022 Hecht Rep. at 1 ("ZHP . . . could have and should have identified the risk of formation of nitrosamines including NDMA and NDEA, and utilized that information to test for and identify, and then prevent the nitrosamine impurities in the valsartan API and finished dose sold by ZHP."); Bain Rep. at 8 (claiming there was "inadequate testing of the drug products due to the failure to test for the foresseable [sic] presence of NDMA and NDEA").)

[85] (*See, e.g.*, 2022 Najafi Rep. at 26 ("DMF solvent often contains dimethylamine. Presence of sodium nitrite and dimethylamine from solvents like DMF can contribute to NDMA formation. HNO_2 is plentiful in this reaction and the manufacturer did not heed the obvious risk of nitrosamine formation.").)

[86] Sheldon RA. (2019) The greening of solvents: Towards sustainable organic synthesis. Current Opinion in Green and Sustainable Chemistry, 18, 13-19.

[87] (ZHP02579969.)

$NaNO_2$ was added, and the pH value of the mixture was adjusted to pH <=3 using HCl (6N) while maintaining the temperature [redacted] °C.[88]

At the time the $ZnCl_2$ process was developed, little was known about the decomposition of DMF solvent to generate a secondary amine dimethylamine. Plaintiffs' experts Najafi, Bain and Hecht cite to *Purification of Laboratory Chemicals*, Armarego, WLF (1996 (Edition 4th), 2009 (Edition 6th),[89] which states that "DMF decomposes slightly at its normal bp [boiling point] (153C) to give small amounts of dimethylamine and CO." Based on my own review of the literature, other isolated references note that "DMF decomposes to generate dimethylamine at >350 C," a significantly higher temperature.[90] Even if these limited references were sufficient to demonstrate that it was well-known in the chemistry world that DMF can degrade, which they are not, they merely describe "slight" degradation at high temperatures. As set forth above, the $ZnCl_2$ process was run at a high of 135 °C, or 18 °C lower than the boiling point of DMF, and then cooled. ZHP had no scientific reason to expect the degradation of DMF, a common solvent, under the reaction condition of 135 °C in light of the limitation in knowledge regarding this chemistry. Indeed, the fact that ZHP did not conduct an extraction to separate the crude Valsartan before adding $NaNO_2$ to quench the excess azide is, in my opinion, direct evidence indicating that ZHP, at the relevant time, had no knowledge about dimethylamine formation from the degradation of DMF solvent.

As noted above, the textbook cited by plaintiffs' experts also states that "DMF decomposition is catalyzed by acidic and basic materials, so that even at room temperature, DMF is appreciably decomposed if allowed to stand for several hours with solid KOH, NaOH, CaH_2".[91] Solid KOH, NaOH, CaH_2 represent strong bases, which create unusually strong basic environments around themselves in solid form. But in the crude Valsartan (step #4) of the $ZnCl_2$ process, where DMF was used, reaction conditions were neutral.

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88 (ZHP02579969.)

89 (*See* 2022 Najafi Rep. at 26; 2022 Hecht Rep. at 5; Bain Rep. at 41.)

90 Farhi M, Morel M, Cavigneaux A (1968) Dimethylformamide $HCON(CH_3)_2$. Cahier de notes documentaires, 50:91–93.

91 *Purification of Laboratory Chemicals*, Armarego, WLF (1996 (Edition 4th)), Page 206.

Plaintiffs' expert Najafi opines that ZHP should have determined the risks because "Knowledge of basic organic chemistry suggests that changes to the chemical reagents of a reaction would alter the degradant/by-product profiles requiring such risks to be critically evaluated. ZHP failed to conduct a thorough risk-based evaluation of the possible formation of nitrosamines resulting from their proposed process changes."[92] When the reaction condition is modified, the by-product profile change is possible. However, in ZHP's $ZnCl_2$ process, the tetrazole formation reaction using $ZnCl_2$ as a catalyst is well-documented in the literature. In fact, a literature search related to the synthetic method to the production of tetrazoles using $ZnCl_2$ as a catalyst on SciFinder generated at least 28 reports, nine of which used DMF as the solvent for the tetrazole formation reaction. Importantly, none of these nine examples mentioned any side reaction caused by the decomposition of the DMF solvent.

In short, plaintiffs' experts have not identified any evidence that, at the time when $ZnCl_2$ process was developed and used, it was reported in the literature that DMF could degrade into dimethylamine in the reaction conditions present in the $ZnCl_2$ process. And plaintiffs' experts certainly have not made a showing that, as of 2011 when ZHP began assessing the $ZnCl_2$ process,[93] it was widely known or expected throughout the field of chemistry that DMF degrades in the conditions used to manufacture Valsartan API. As a result, there is no scientific support for plaintiffs' experts' assertions that ZHP should have expected that a secondary amine such as dimethylamine would result from the use of DMF solvent in the reaction process. And without a secondary amine, NDMA and other nitrosamines cannot form. In other words, without knowing the possible formation of dimethylamine in the $ZnCl_2$ process via the decomposition of DMF solvent, there was no means to have a secondary amine generated in the reaction. Therefore, in my opinion, ZHP would not have reasonably foreseen the formation of a nitrosamine impurity.

Second, even if a secondary amine were an expected part of the $ZnCl_2$ process, nitrosamine formation from nitrous acid and secondary amine is a documented but rather uncommon reaction that even experienced chemists may not have learned – and was not generally known in the field of chemistry a decade ago. While this reaction was brought to my personal attention as a result of my significant work on an nNOS inhibitor project at Northwestern University, this is an area of

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92 (2022 Najafi Rep. at 27; *see also id*. at 24.)

93 (*See, e.g.*, ZHP01843066-ZHP01843067.)

particularized research that is not, as plaintiffs' experts suggest, basic chemistry.[94] I have been a professor of Chemistry for 13 years and have never once in that time taught this reaction in either my undergraduate (e.g., Organic Chemistry I and Organic Chemistry II) or graduate courses (e.g., Organic Synthesis in Drug Design and Medicinal Chemistry). In addition, in the past 11 years working in my own research lab and studying potential carcinogens, I have never used this reaction in any of my projects.

In light of the above, it is reasonable and appropriate that ZHP would not have known, even after its complete and appropriate risk assessment, about the possibility of the formation of the secondary amine dimethylamine that could potentially react with nitrous acid to form nitrosamine NDMA. As a result, the fact that ZHP did not specifically investigate the potential for NDMA formation does not render the company's risk assessment for the $ZnCl_2$ process inadequate.

B. ZHP Performed Reasonable And Appropriate Risk Assessments For The TEA Process With Quenching.

A review of company documents and regulatory filings makes clear that ZHP properly conducted a multi-phase investigation of the risks of the TEA process with quenching before the process was used to manufacture Valsartan API. Plaintiffs' experts lack scientific support for the notion that it was well documented that the reaction of a tertiary amine TEA and nitrous acid ($NaNO_2$ + HCl solution) would produce NDEA (see **Figure 9**, above) at the time when the TEA process with quenching was analyzed. Even today, a review of the relevant literature makes clear that such a reaction is complex and was not easily foreseeable.

1. ZHP Properly Conducted A Multi-Step Risk Analysis For The TEA Process With Quenching.

The synthetic route of the TEA process with quenching is shown in **Figure 10** below. Compared to the previous TEA process without quenching, several changes were made.

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[94] (*See, e.g.*, 2022 Najafi Rep. at 7 ("Basic chemistry principles instruct us that secondary amine in the presence of nitrite and acid predictably and readily react to produce genotoxic nitrosamines such as NDMA and NDEA."); 2022 Hecht Rep. at 7 ("ZHP simply ignored or didn't understand this basic chemistry.").)

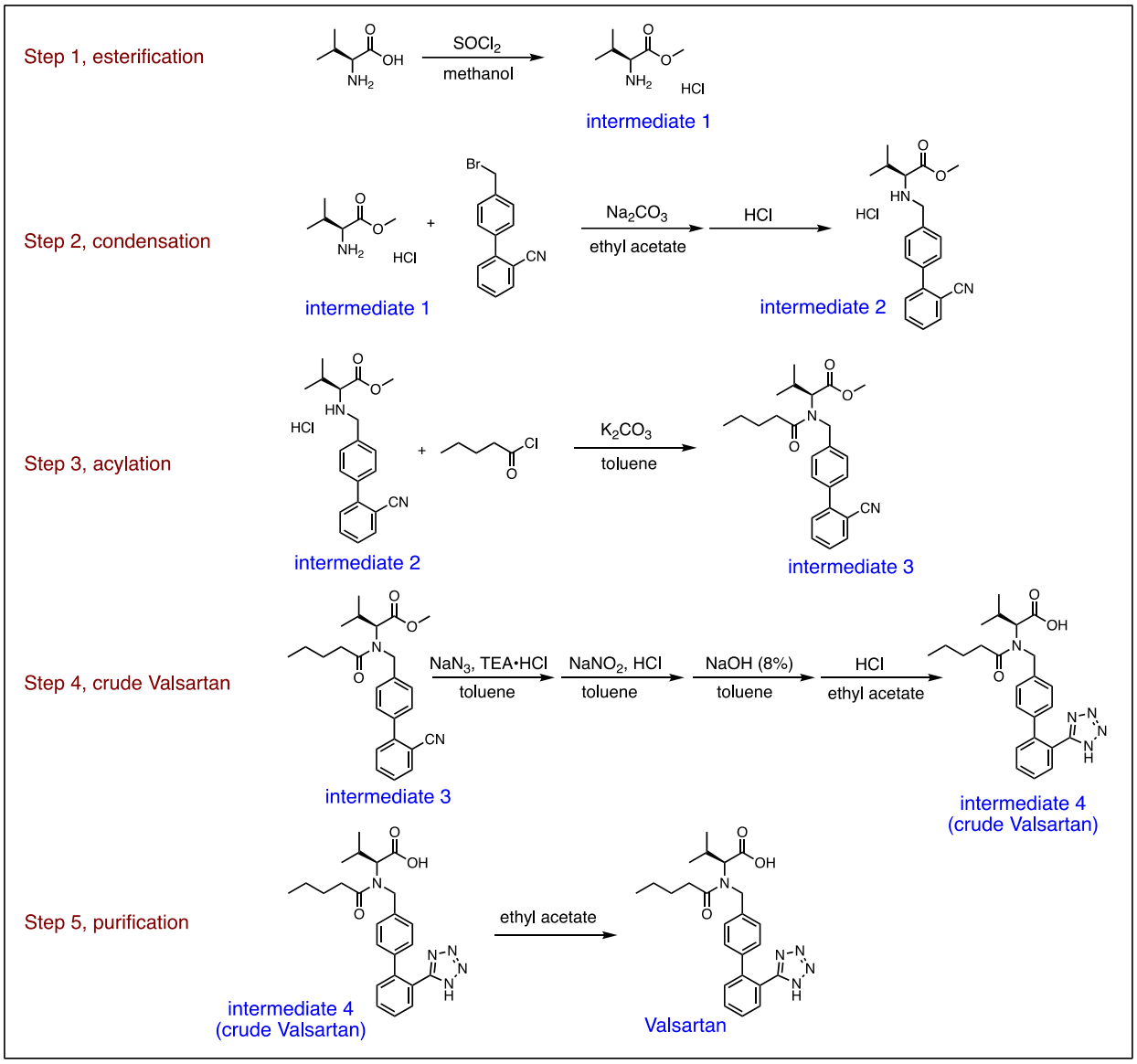

Figure 10. The synthetic route of the TEA process with quenching.

1. Both Steps 1 and 2 (**Figure 10**, above) were optimized to lower the cost and improve the production environment, while no change was made to the synthetic route.

In the previous process, intermediate 1 (**Figure 10**, above) was formed and suspended in ethyl acetate before centrifugation and drying. Ethyl acetate was used to enhance the liquidity of the produced intermediate 1 in a format of slurry to improve the transfer from reactors. However, intermediate 1 does not dissolve and crystallize well in ethyl acetate. Importantly, ethyl acetate also has the potential to introduce an impurity (an ethyl-condensation product via an ester exchanging) to the reaction. Therefore, the slurry operation to intermediate 1 using ethyl acetate

was deleted in the TEA process with quenching. This change had no negative impact on quality attributes.

Given the simplicity of the reaction that produces intermediate 1 (Step 1), as well as the fact that this reaction takes place early in TEA process, the centrifugation and drying operations for intermediate 1 were canceled to avoid the EHS concern that hydrochloric gas (HCl_g) could form during the centrifugation and subsequent drying operations. At the same time, the non-significant specification for intermediate 1 was also canceled and the significant quality control for intermediate 2 remained the same.

The use of potassium carbonate (K_2CO_3) in Step 2 (**Figure 10**, above) of the synthetic route was replaced by sodium carbonate (Na_2CO_3). This was a non-functional replacement of reagent to reduce the cost of the reaction, while the synthetic route for manufacturing did not change.

Comparing the previous processes, the modified process produced similar yields of intermediate 2 and reduced impurity levels, as shown in **Table-1** below.[95]

Table-[AUTONUM * Arabic] Batch Analysis Data of Consecutive 3 Batches
Intermediate 2 (pilot scale)

Batch No.	Yield	**Ethyl-condensation**	Any other impurity (max.)	Total impurities
Currently adopted process (pilot scale)				
C20204-11-031	85.29%	**0.05%**	0.08%	0.13%
C20204-11-032	86.81%	**0.01%**	N.D	0.01%
C20204-11-033	85.76%	**0.01%**	0.01%	0.03%
Original process				
C20207-10-001	85.8%	**0.45%**	0.02%	0.5%
C20207-10-002	82.0%	**0.30%**	0.03%	0.3%
C20207-10-003	89.0%	**0.25%**	0.05%	0.3%

2. <u>After the acylation reaction (Step 3, **Figure 10**, above), a washing procedure was added during the post-processing operation.</u>

Before the washing procedure using water and saturated sodium chloride (NaCl) solution, an additional washing procedure was added (after the reaction was complete) using sodium hydrogen carbonate ($NaHCO_3$) solution to the reaction mixture. This additional $NaHCO_3$ washing increased the pH value and decreased the risk of acidic substance from this step (Step 3) in later synthetic steps of the process. There was no adverse change in qualitative and quantitative profiles.

95 (PRINSTON00079751.)

3. While the synthetic route remained the same, changes were made to Step 4 (**Figure 10**, above) to reduce the racemization (*see*, **Figure S1**, above) and lower the cost.

The specific changes included: 1) decreasing the molar ratio of azide used for the reaction from 2 to 1.5; 2) adding a quenching procedure after the tetrazole formation reaction with a mixture of sodium nitrite ($NaNO_2$) and HCl solution; 3) replacing potassium hydroxide (KOH) with sodium hydroxide (NaOH) in the hydrolysis procedure; and 4) canceling the drying of intermediate 4 (crude Valsartan) and consequently canceling the assay limit for intermediate 4 (crude Valsartan) due to wet substance.[96]

The original molar ratio of raw material and azide was 1:2. Although the large excess of azide could increase the yield of the reaction, the excess azide could also increase the racemization to form D-Valsartan (*see*, **Figure S1**, above). Thus, the molar ratio of raw material and azide was changed to 1:1.5. In light of the possibility that excess azide left over after the tetrazole formation reaction could introduce acidic azide, a highly toxic gas that can raise EHS concern during manufacturing, a quenching procedure was added after the tetrazole formation reaction using $NaNO_2$ and HCl solution. This quenching procedure was added to ensure the excess azide in the reaction mixture was destroyed completely. It minimized the risk of residual azide carry-over into the final Valsartan API and the environment. As shown in **Table-2** below, the batch results indicated that no residual azide or nitrite was detected in the finished drug substance.[97]

Table-[AUTONUM * Arabic] Batch Analysis Data of Residual Azide and Nitrite in Finished Drug Substance

Batch No.	Quality	Manufacturing Date	Residual nitrite	**Residual azide**
LOQ	—	—	3ppm	**0.5ppm**
Currently adopted process (single batch, **workshop1**)				
C5354-11-011	300.8 kg	2011.07.02	N.D	N.D
C5354-11-012	300.4 kg	2011.07.03	N.D	<LOQ
C5354-11-013	300.6 kg	2011.07.04	N.D	<LOQ
Currently adopted process (single batch, **workshop2**)				
C2210-11-145	152.34 kg	2011.08.28	N.D	N.D
C2210-11-146	151.86 kg	2011.08.29	N.D	N.D
C2210-11-147	151.74 kg	2011.08.31	N.D	N.D

In addition, to reduce the overall cost, potassium hydroxide (KOH) previously used in Step 4 (**Figure 10**, above) was replaced with sodium hydroxide (NaOH). This is a non-functional

96 (PRINSTON00079751-PRINSTON00079752.)

97 (PRINSTON00079753.)

replacement of the strong hydroxide base used in the hydrolysis procedure (*see*, **Figure S1**, above). The synthetic route for manufacturing did not change. After the change from KOH to NaOH, the reaction condition was developed by varying the reaction temperature and time (**Table-3** below). The optimized condition was 35-40 ºC for 3.5-5 hours (**Table-3** below).[98]

Table-[AUTONUM * Arabic] Reaction Temperature and Time for Saponification in Step 4 (Proposed process)

Time	30 min		70 min		140 min		210 min		320 min	
Temp.	Enan-tiomer	Valsartan	Enan-tiomer	Valsartan	Enan-tiomer	Valsartan	Enan-tiomer	Valsartan	Enan-tiomer	Valsartan
50°C	2.72%	50.56%	6.56%	91.89%	—	—	—	—	—	—
45°C	2.065%	45.05%	4.67%	88.45%	6.5%	92.20%	—	—	—	—
40°C	1.91%	47.59%	3.21%	68.65%	5.47%	91.52%	**5.61%**	**92.88%**	—	—
35°C	1.44%	31.31%	2.5%	58.17%	3.91%	76.30%	**5.90%**	**92.37%**	6.51%	92.58%
30°C	—	—	1.34%	38.51%	2.34%	57.90%	4.28%	79.65%	5.0%	92.00%

Conclusion: To obtain the percent conversion (%Valsartan) basically at 92-93% from saponification in step 4, the reaction temperature and reaction time should be controlled at 35-40°C and 3.5-5 hours

via experiments matrix. The controlled process parameters could meantime hold up the increasing of enantiomer compared to 7-8% existed in reaction solution according to currently original process.

Racemization could happen in Valsartan synthesis at the chiral carbon center (*see*, **Figure S1** blue star labeling, above) during the manufacturing process, especially in Step 4 (**Figure 10**, above). The racemization of the compound can be enhanced during a drying procedure. Thus, cancellation of the drying could reduce the risk of racemization. Other than the cancellation of the drying, intermediate 4 (crude Valsartan) isolation by centrifugation did not change. The in-process material control for intermediate 4 (crude Valsartan) also did not change. Moreover, the same solvent (ethyl acetate) was used for recrystallization. Therefore, the cancellation of the drying procedure for intermediate 4 (crude Valsartan) was considered to have minimal impact on the quality of the product. Because, after the change, the intermediate is a wet substance, the original assay limit (>= 80%) was consequently removed (**Table-4**, below). The test procedure for the assay was retained. The results from the tests were used to determine material charging as "dried basis" in the later crystallization step.[99]

98 (PRINSTON00079753.)

99 (PRINSTON00079754.)

Table-[AUTONUM * Arabic] Specification of Crude Valsartan from Current Process (change in green)

Crude Valsartan	**Original Process**	**Currently adopted Process**
Test item	Acceptance Criteria	Acceptance Criteria
Appearance	White to yellowish powder	White to yellowish solid
Impurity A (HPLC)	≤ 5.0%	≤ 5.0%
Related substances (HPLC)		
Impurity B	≤ 0.25%	≤ 0.25%
Impurity C	≤ 0.5%	≤ 0.5%
RRT 1.7 impurity	≤ 1.0%	≤ 1.0%
Any other single impurity	≤ 0.5%	≤ 0.5%
Total impurities apart from impurity A	≤ 2.0%	≤ 2.0%
Purity (HPLC)	—	≥ 98.0%
Assay (Titration)	**≥ 80.0%**	**For information**

4. In Step 5 (**Figure 10**, above), the yield was adjusted to 70.5-82.5%.

The changes include: 1) using the crude Valsartan with dried basis (weight of wet substance multiplied by its assay) as the integrated quantity of wet substance for charging; and 2) adjusting the yield of Step 5 (**Figure 10**, above) from 60.0-70.0% to 70.5-82.5% using the quantity of intermediate 4 (crude Valsartan) with dried basis. Note: this change only reflected the calculation pattern reforming, but did not cause change in the actual yields.[100]

In sum, testing of the TEA process with quenching demonstrated that the specification of final substance Valsartan did not change as a result of this process change. There was no adverse change in its qualitative and quantitative impurity profile. The route for the synthesis did not change. All intermediates remained the same. There were no new functional reagents, catalysts, or solvents added into the process.

2. ZHP Did Not Have Reason To Investigate The Possibility Of NDEA Formation As Part Of Its Risk Assessment For The TEA Process With Quenching.

Plaintiffs' experts opine that ZHP should have known that NDEA formation was a possible result of the TEA process with quenching, and therefore a proper risk assessment would have

100 (*Id.*)

specifically investigated whether any of the trace-level impurities in Valsartan API, which FDA regulations did not require it to identify, were NDEA.[101]

According to plaintiffs' experts, ZHP should have known that the use of triethylamine hydrochloride salt (TEA•HCl) as a catalyst in the TEA process with quenching created a risk of nitrosamine NDEA formation because TEA can react with nitrous acid ($NaNO_2$ + HCl solution) to create NDEA. However, the reaction of TEA and nitrous acid ($NaNO_2$ + HCl solution) to form NDEA was not reasonably foreseeable at the time the TEA process with quenching was assessed.

As set forth in detail above, NDEA formation requires the presence of a secondary amine diethylamine (**5a**, *see*, **Figure 9**, above) along with NO^+ (**4**) generated from nitrous acid (or sodium nitrite + inorganic acid). (*See*, **Figure 5**, above.) TEA, a tertiary amine, is one of the common non-nucleophilic bases that have been used in organic synthesis. TEA is not a secondary amine. It cannot react with nitrous acid via a similar mechanism as that for a secondary amine (*see*, **Figure 5**, above) to produce the nitrosamine NDEA. Instead, TEA must first be converted into the secondary amine diethylamine (**5a**) via a multi-step mechanism before it can react with NO^+ (**4**) to form NDEA in the crude Valsartan (step #4) of the TEA process with quenching (*see*, **Figure 9**, above). This reaction is known to be very slow.[102,103] In the TEA process with quenching, the tetrazole formation reaction was done by mixing the starting material with NaN_3 in the presence of TEA•HCl at 93-95 ℃ for 20 hours.[104] After cooling the mixture to 35 ℃, $NaNO_2$ was added and then the pH value of the mixture was adjusted to pH <=3 using HCl (6N) while maintaining the temperature <10 ℃.[105]

At the time when the TEA process with quenching was developed, little was known about the possibility that a reaction between TEA and nitrous acid (or sodium nitrite + inorganic acid)

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101 (*See, e.g.*, 2022 Najafi Rep. at 28 ("ZHP's risk assessment should have led them to monitor formation of multiple potential nitrosamines including NDMA and NDEA."); 2022 Hecht Rep. at 1 ("ZHP . . . could have and should have identified the risk of formation of nitrosamines including NDMA and NDEA, and utilized that information to test for and identify, and then prevent the nitrosamine impurities in the valsartan API and finished dose sold by ZHP."); Bain Rep. at 8 (claiming there was "inadequate testing of the drug products due to the failure to test for the foresseable [sic] presence of NDMA and NDEA.").)

102 Smith PAS, Loeppky RN. (1967). Nitrosative cleavage of tertiary amines. *J. Am. Chem. Soc.* 89, 1147-1157.

103 Smith PAS, Pars HG. (1959). Nitrosative cleavage of N',N'-dialkhylhydrazides and tertiary amines. *J. Org. Chem.* 24, 1325-1332.

104 (ZHP02579969.)

105 (ZHP02579969.)

could generate the nitrosamine NDEA. The reaction of TEA with nitrous acid (or sodium nitrite + inorganic acid) is not generally known among all chemists. During my 13-year career as a professor of Chemistry, I have never taught this reaction in either my undergraduate (e.g., Organic Chemistry I and Organic Chemistry II) or graduate courses (e.g., Organic Synthesis in Drug Design and Medicinal Chemistry). In addition, in the past 11 years working in my own research lab and studying potential carcinogens, I have never used this reaction in any of my projects. In fact, despite my substantial experience in the field of chemistry, I was not aware of the possibility of this reaction prior to my involvement in this case.

Plaintiffs' experts fail to cite references regarding the reaction of TEA with nitrous acid (or sodium nitrite + inorganic acid). Based on my own review of the literature regarding the synthetic method to the production of NDEA from TEA on SciFinder,[106] only 10 publications were found. Note that common reactions are typically reported in tens of thousands of publications. Moreover, none of these 10 journal articles addresses the use of nitrous acid (or sodium nitrite + inorganic acid) and TEA to produce NDEA. Instead, all the published methods included a special nitrosating reagent such as the Fremy's salt,[107] nitric acid/acetic anhydride,[108] N_2O_3,[109] and N_2O_4[110] to facilitate the formation of NDEA. Therefore, plaintiffs' experts have not identified any evidence that, at the time of the development of the TEA process with quenching, it was reported in the literature that TEA could react with nitrous acid (or sodium nitrite + inorganic acid) to form NDEA under the conditions present in the TEA process with quenching. And plaintiffs' experts certainly have not made a showing that, as of 2012, when ZHP updated its regulatory filings to include TEA process with quenching as a manufacturing process, it was commonly known or

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[106] SciFinder is produced by Chemical Abstracts Service (CAS). It is the most comprehensive database for the chemical literature. SciFinder can search by topic, author, substances (by name or CAS Registry Number). In addition, one can also use the editor feature to draw chemical structures, substructures, or reactions. SciFinder is a core research tool for chemistry, chemical engineering, materials science, and other science and engineering disciplines.

[107] Castedo, Luis; et al, (1983) Fremy's salt (potassium nitrosodisulfonate): a nitrosating reagent for amines. 6, 301-302.

[108] Boyer JH, Pillai TP, Ramakrishnan VT. (1985) Nitrosamines and nitramines from tertiary amines. Synthesis, 677-679.

[109] Rosadiuk, Kristopher A.; et al, (2018) Isolable Adducts of Tertiary Amines and Dinitrogen Trioxide. European Journal of Inorganic Chemistry, 41, 4543-4549.

[110] Boyer, Joseph H.; et al, (1985) Nitrosamines from tertiary amines and dinitrogen tetraoxide. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999), (8), 1661-4.

expected in the field of chemistry that TEA reacts with nitrous acid (or sodium nitrite + inorganic acid) under the conditions used at ZHP to manufacture Valsartan API. As a result, there is no scientific support for plaintiffs' experts' assertions that ZHP should have expected that the catalyst TEA•HCl in the reaction process would react with the quenching agent (sodium nitrite + inorganic acid) to result in the formation of nitrosamine NDEA. For these reasons, ZHP would not have reasonably foreseen the formation of a nitrosamine impurity.

In sum, it is reasonable and appropriate that ZHP would not have known, even after its appropriate risk assessment for the TEA process with quenching, about the possibility of a reaction between the catalyst TEA•HCl and the quenching agent (sodium nitrite + inorganic acid) in the reaction procedure that could lead to the formation of the nitrosamine NDEA. As a result, the fact that ZHP did not specifically investigate the potential for NDEA formation does not render the company's risk assessment for the TEA process with quenching inadequate.

VI. ZHP Performed Adequate Testing While Valsartan Was On The Market.

Gas chromatography (GC) is a type of chromatography that is widely used in analytical chemistry for separating and analyzing organic compounds that can be vaporized without decomposition.[111] It is routinely used in testing the purity of a substance.[112] GC achieves the separation of different compounds in a mixture by injecting a sample (either gaseous or liquid) into a mobile phase (called the carrier gas, usually an inert gas such as helium, argon, or nitrogen) and passing through a stationary phase (called the column, which is made of glass or metal tubing containing a microscopic layer of viscous liquid on a surface of inert solid-supported particles). The column is located in an oven so that its temperature can be controlled. The eluent coming off the column is usually followed by a coupled detector such as flame ionization detector (FID) and mass spectrometry (MS).

FID is an analytical instrument that measures analytes in a gas stream. It functions by detecting ions that are formed during combustion of organic compounds in a hydrogen flame. The generation of the ions in the testing sample is proportional to the concentration of each organic

[111] Harvey, David (2000). Modern Analytical Chemistry. Boston: McGraw-Hill.

[112] Pavia, L., Gary M. Lampman, George S. Kritz, Randall G. Engel (2006). Introduction to Organic Laboratory Techniques (4th Ed.). Thomson Brooks/Cole. pp. 797–817.

component in the gas stream.[113] To complete the detection, a potential difference is generated by two electrodes. The positive electrode generates the flame, while the negative electrode, commonly called the collector plate, locates above the flame. The ions generated from the positive electrode are attracted to and eventually hit the collector plate, to induce a current that can be measured and recorded as peaks on a plot of total ion (y-axis) against time (x-axis). The detected current correlates with the proportion of the reduced carbon atoms in the flame. The measurement of ion per time unit makes FID a mass-sensitive instrument.[114]

FID is the most widely and successfully used GC detector for volatile hydrocarbon organic compounds.[115] Gas chromatography coupled with flame ionization detection (GC-FID) is commonly used in separating and analyzing organic compounds that can be vaporized without decomposition. It is powerful since it can detect almost all carbon-containing organic molecules. As an alternative method to GC-FID, GC-MS is an analytical method that combines GC and MS to identify different organic components within a testing sample.[116]

As a professor, I have done significant work in testing samples (either as a single organic compound or as a mixture of different organic compounds) that were generated from various reaction types. Because FID is the most widely and successfully used GC detector, it is my opinion that it was appropriate for ZHP to use GC-FID to test for impurities in a chemical substance such as Valsartan API.

According to plaintiffs' experts, ZHP should have tested for the presence of NDMA and NDEA as part of the manufacturing process.[117] As explained above, the presence of either NDMA or NDEA was not reasonably foreseeable at the time the $ZnCl_2$ process and the TEA process with quenching were assessed. NDMA formation requires the presence of a secondary amine along with NO^+ (**4**) generated from nitrous acid (or sodium nitrite + inorganic acid). (*See*, **Figure 5**,

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113 Skoog DA, Holler FJ, Crouch ST. Principles of Instrumental Analysis.

114 *Id.*

115 Zhu X, Sun J, Ning Z, Zhang Y, Liu J. (2016) High performance mini-gas chromatography-flame ionization detector system based on micro gas chromatography column. Review of Scientific Instruments 87, 044102.

116 Sparkman DO, Penton Z, Kitson FG (2011). Gas Chromatography and Mass Spectrometry: A Practical Guide. Academic Press.

117 (2022 Najafi Rep. at 26 ("The QC department should have been alerted by the chief process chemist to monitor for nitrosamine impurities as part of the manufacturing process").)

above.) DMF is one of the common organic solvents that have been used in organic synthesis.[118] It is not a secondary amine and cannot react with nitrous acid to result in NDMA. Instead, DMF is a solvent that was used in the crude Valsartan (step #4) of the $ZnCl_2$ process. On the other hand, NDEA formation requires the presence of a secondary amine such as diethylamine (**5a**, *see*, **Figure 9**, above) along with NO^+ (**4**) generated from nitrous acid (or sodium nitrite + inorganic acid). (*See*, **Figure 5**, above.) TEA is a tertiary amine used in the tetrazole formation reaction in the TEA process with quenching as a catalyst. TEA cannot react with nitrous acid via a similar mechanism as that for a secondary amine (*see*, **Figure 5**, above) to produce the nitrosamine NDEA. Instead, TEA must first be converted into the secondary amine diethylamine (**5a**) via a multi-step mechanism before it can react with NO^+ (**4**) to form NDEA in the crude Valsartan (step #4) of the TEA process with quenching (*see*, **Figure 9**, above).

At the time when the $ZnCl_2$ process was developed and used, little was known about the decomposition of the DMF solvent to generate a secondary amine dimethylamine, which could further react with nitrous acid (or sodium nitrite + inorganic acid) to generate a nitrosamine NDMA. Similarly, at the time when the TEA process with quenching was developed, little was known about the reaction of TEA with nitrous acid (or sodium nitrite + inorganic acid) to generate a nitrosamine NDEA. Because it was not established that there was an inherent risk of nitrosamine formation, in my opinion, it is reasonable that ZHP did not specifically test for these as part of its manufacturing processes.

Plaintiffs' experts also state that five testing methods for nitrosamines were available, and any reasonable organic chemists would have used one of them to test Valsartan API for nitrosamines.[119] The five methods identified by plaintiffs' experts include the combined

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[118] Sheldon RA. (2019) The greening of solvents: Towards sustainable organic synthesis. Current Opinion in Green and Sustainable Chemistry, 18, 13-19.

[119] (2022 Najafi Rep. at 9-10 ("In response to the detection of nitrosamines found in valsartan containing medications, the FDA published testing methods with several options for industry, as well as regulators, to test for nitrosamines, including NDMA and NDEA. These FDA methods included the following: (a) Combined headspace method: a GC-MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and n-nitrosodiethylamine (NDEA) simultaneously; (b) Combined direct injection method: a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously; (c) Direct injection GC-MS method: a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and n-nitrosodibutylamine (NDBA); (d) Headspace GC-MS method: a method that can detect NDMA, NDEA, ndipa, and neipa; and (e) lc-hrms method: a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)"); *id.*at 10 ("All these testing methods have existed for decades, long before the

headspace method (GC-MS method), combined direct injection method (GC-MS/MS method), direct injection (GC-MS method), headspace (GC-MS method), and LC-HRMS method. All of these methods use MS as the detector. Although these MS-based methods are sensitive towards the nitrosamines NDMA and NDEA, I have not seen any evidence that they were the standard in the industry at the time when the $ZnCl_2$ process and the TEA process with quenching were being utilized for the production of Valsartan API and, as I have explained above, ZHP did not have a scientific reason to be looking for NDMA or NDEA in Valsartan API at that time. Furthermore, I understand that GC-FID had been the standard in the industry (including by Novartis, which ultimately identified NDMA in Valsartan API in 2018). Therefore, it was reasonable that ZHP used GC-FID as its testing method for Valsartan API.

VII. Plaintiffs' Experts Have Not Presented Evidence That ZHP Employees Were Aware Of The Possibility Of NDMA Or NDEA Resulting From Its Manufacturing Processes Prior To 2018.

Plaintiffs' experts assert that, in an email dated July 27, 2017, ZHP employee Jinsheng Lin "acknowledged the impurity he was investigating [in crude irbesartan] was very likely an 'N-NO compound' which 'is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite.'"[120] They opine that this email rebuts "ZHP's argument that it did not have that information [about the possible nitrosamine contamination of Valsartan API] until June 2018.[121] In fact, Mr. Lin's email demonstrates that ZHP did not have reason to know about the potential for NDMA or NDEA resulting from the $ZnCl_2$ process or TEA process with quenching.

ZHP manufacturing processes using sodium nitrite were developed or used for the commercial production"); Bain Rep. at 74 ("In addition, the technology to test for nitrosamine impurities existed, was well known, and should have been applied to determine whether nitrosamines were forming. If those steps had been taken as required, the process validation specifications would have included testing for NDEA and NDMA, and the NDEA and NDMA formed during the manufacturing process, as well as that resulting from cross-contamination due to inadequate cleaning of shared production lines would have been identified"); 2022 Najafi Rep. at 28 ("In my opinion, the only reason one would choose to use a GC-FID instead of GC-MS would be a lack of understanding of chemical processes and reactions, and/or to reduce chances of detection of finding impurities").)

120 (2022 Najafi Rep. at 30-31 (citing 4/20/2021 Min Li Dep. Ex. ZHP-296; ZHP00190573-ZHP00190574).)

121 (*See* Bain Rep. at 1 ("ZHP apparently had knowledge as of July 27, 2017 or earlier of the NDMA impurities and that the root cause of nitrosamine contamination in sartans was the quenching with sodium nitrite."); Plunkett Rep. at 32 (claiming that the July 27, 2017 email "shows that ZHP understood at least by 2017 that nitrosamines were created in the production generally of ZHP's sartan APIs.").)

Mr. Lin's email relates to the discovery of a hypothetical nitrosated impurity in the lab-scale production of Irbesartan, a different drug molecule than Valsartan API. In the email, Mr. Lin also mentions impurity K, a nitrosated impurity of the deacylated Valsartan, also a different drug molecule from Valsartan API (**Figure 11**), which was described in a 2013 patent. (Zhejiang Second Pharma Co. Ltd.) Mr. Lin's email is written in Chinese, my native language. Based on my understanding of Chinese and my expertise as a chemist, it is obvious to me that Mr. Lin's email reports the potential for a type of nitrosation reaction that happens between a reactive nitrogen atom on a drug product or a drug intermediate (**Figure 11**, green circled) and a nitrosonium ion (NO^+). As demonstrated in **Figure 11**, both Irbesartan and deacylated Valsartan, which are referenced in the email, contain a reactive nitrogen atom on the drug molecule itself, which can react with NO^+ to form nitrosated impurities. However, a similar reaction cannot take place on acylated (step #3) product in the $ZnCl_2$ process because no reactive nitrogen atom is present in the chemical structure of the starting material. The email makes no reference to possible nitrosamine formation from the TEA process with quenching or the $ZnCl_2$ process for Valsartan API.

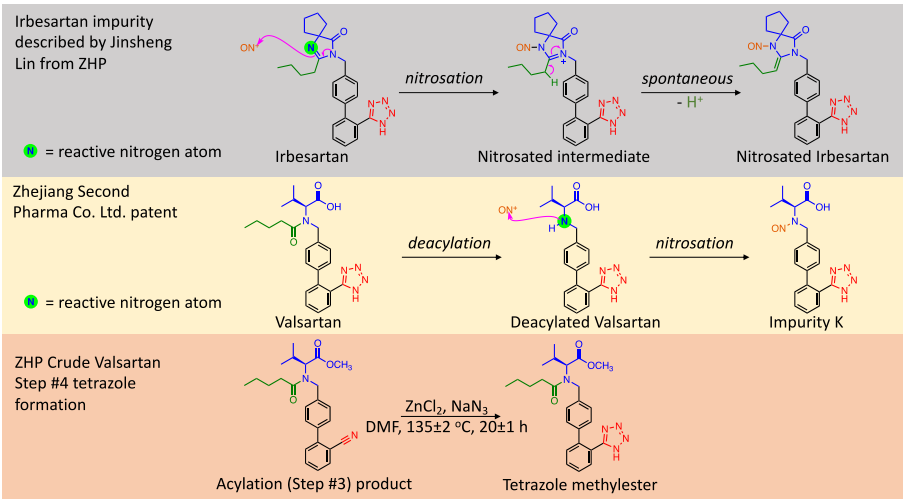

Figure 11. Proposed mechanism for the formation of nitrosated Irbesartan (top) and impurity K (middle) described in Jinsheng Lin's July 17, 2017 email, as compared to the tetrazole formation conditions in the manufacture of Valsartan API (bottom).

In addition, ZHP employees who have testified about the email have made clear that "due to insufficient extent and depth of process research at the early stage, as well as insufficient study

and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied" with respect to Irbesartan, and therefore ZHP "was unaware of the further reaction between degradation products and raw material" related to Irbesartan.[122] As a result, Mr. Lin's email discussing Irbesartan could not have been addressing the formation of nitrosamines as a result of the potential degradation of DMF, which is what plaintiffs' experts assert resulted in the formation of nitrosamines during the $ZnCl_2$ process for Valsartan API. In fact, the email demonstrates that, when discussing potential nitrosamine formation, Mr. Lin did not have a reason to raise the issue of degradation during manufacturing processes for Valsartan API because ZHP did not know these processes could potentially result in nitrosamines.

Correspondence between ZHP and Novartis in May and June 2018 further demonstrates that ZHP was unaware of the potential for nitrosamine formation in its Valsartan API prior to that time. First, neither ZHP nor Novartis – which contacted ZHP on May 22, 2018 about the peaks that were ultimately identified as NDMA – initially knew what those peaks were.[123] And when Novartis asked for additional support for the identification of the peaks, ZHP ran a GC-MS analysis, but did not discover the NDMA at first.[124] It was not until several weeks after the initial communication that Novartis and ZHP were able to confirm that NDMA was present in the Valsartan API.[125] Novartis noted "how exceptional [ZHP's] support [had] been through" the process of identifying the unknown peaks.[126]

The difficulty ZHP and Novartis encountered in identifying NDMA is unsurprising. In the months after ZHP announced the recall of Valsartan API, even the FDA acknowledged that NDMA is difficult to identify and that neither the FDA nor the industry knew to test for it – or how to best test for it. According to the FDA's public statement about Valsartan on August 30, 2018:

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122 (4/22/2021 Min Li Dep. Tr. 528:14-531:4.)

123 (*See, e.g.*, ZHP02172439 (initial email from Novartis stating that "[d]uring our analysis of residual solvents by GC (using a combined method) at Novartis we have found a number of solvents that we cannot identify for the following batches"); ZHP00389307-ZHP00389308 (initial response to Novartis from ZHP suggesting that the unknown peaks were "dimethyl sulfide" and the product of a "reaction between Valsartan and DMSO").)

124 (*See* ZHP00389306 (ZHP providing "the chromatogram of GC-MS & Identification as attached").)

125 (ZHP01875822.)

126 (ZHP01875820.)

> [T]he FDA maintains the most advanced pharmaceutical laboratory of any regulatory agency in the world. As soon as we were aware of the NDMA impurity in certain valsartan drugs, we began collecting samples of all valsartan API and products marketed in the U.S. ***At the same time, our scientists began developing a test to detect and quantify NDMA in valsartan API. NDMA's properties make it difficult to find.*** [127]

The FDA statement also noted that, "[t]o determine if valsartan products do contain this impurity, ***CDER's scientists have now developed the gas chromatography-mass spectrometry (GC/MS) headspace testing method***. We posted this method to the web to help manufacturers and regulators detect NDMA in valsartan API and tablets." [128] The FDA acknowledged that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it" and regulatory investigators would not know to look for it.[129]

To summarize: one of the most advanced laboratories in the world initially struggled to develop the correct process to identify NDMA in Valsartan given the difficulty of detecting it, even with advanced methods. The FDA also acknowledged that it was not anticipated that NDMA would occur in the Valsartan manufacturing process, meaning that manufacturers and the FDA would not know to test for it. In addition, FDA scientists only developed a gas chromatography-mass spectrometry (GC/MS) headspace testing method specifically designed to test for nitrosamines after NDMA was identified in May 2018. This is consistent with my opinions above.

It is also worth emphasizing that ZHP voluntarily reported the presence of NDMA to the FDA, and also voluntarily recalled its Valsartan API products. It was only after ZHP's voluntary disclosure and recall that the FDA started to look for NDMA in Valsartan-containing drugs and eventually came up with a testing method for NDMA.

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127 *See* U.S. FDA, FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings (current as of 8/30/2018) (available at https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current).

128 *Id*. (emphasis added).

129 *Id.*

Signed on the 22nd day of December, 2022.

Fengtian Xue, Ph.D.

Exhibit A

Exhibit A - Materials Reviewed and Considered

1. Third Amended Consumer Economic Loss Class Action Complaint, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, November 1, 2021
2. Expert Report of Stephen S. Hecht, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, July 6, 2021
3. Expert Report of Stephen S. Hecht, Ph.D, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022
4. Expert Report of Ron Najafi, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, November 4, 2021
5. Expert Report of Ron Najafi, Ph.D., *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022 and all documents cited therein
6. Expert Report of Laura M. Plunkett, Ph.D., DABT, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022
7. Expert Report of Susan Bain, DRSc, *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*, No. 1:19-md-2875-RBK, United States District Court, District of New Jersey, October 31, 2022
8. Interview with Li, Min
9. Interview with Ge, Jucai
10. Interview with Lin, Jinsheng
11. Li, Min Deposition Transcript and Exhibits, April 20, 2021
12. Li, Min Amended Deposition Transcript and Exhibits, April 20, 2021
13. Li, Min Deposition Transcript and Exhibits, April 21, 2021
14. Li, Min Deposition Transcript and Exhibits, April 22, 2021
15. U.S. FDA, Drug Master Files (DMFs) (current as 10/24/2022) (available at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs)
16. U.S. FDA, Information about Nitrosamine Impurities in Medications (available at https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)
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Exhibit B

December 18, 2022

NAME Fengtian Xue, Ph.D.

TITLE Associate Professor

EDUCATION

B.S. Department of Chemistry, 1996-2001
University of Science and Technology of China (USTC)
Anhui, China,
Thesis: Synthesis and Characterization of Polymer-Based Optical Fibers
Supervisor: Dr. Qijin Zhang

Ph.D. Department of Chemistry, 2001-2007
Brown University
Providence, RI
Thesis: Small Molecule Inhibitors for the Serine Protease Plasmin
Supervisor: Dr. Christopher T. Seto

WORK EXPERIENCE

2007 – 2009 Postdoctoral Fellow
Department of Chemistry
Northwestern University
Evanston, Illinois
Project: nNOS Inhibitors for Neurodegenerative Diseases
Supervisor: Dr. Richard B. Silverman

2009 – 2011 Assistant Professor
Department of Chemistry
University of Louisiana at Lafayette
Lafayette, LA

2011 – 2018 Assistant Professor
Department of Pharmaceutical Sciences
School of Pharmacy
University of Maryland Baltimore
Baltimore, MD

2018 – Associate Professor
Department of Pharmaceutical Sciences
School of Pharmacy
University of Maryland Baltimore
Baltimore, MD

RESEARCH INTERESTS

Pre-clinical development of small molecule therapeutics for bacterial infections, AUD, neurodegenerative diseases, and cancer

AWARDS AND PRIZES

2022	NEXUS Award, JHU-UMB Collaborations for Drug Discovery and Development
2020	NEXUS Award, JHU-UMB Collaborations for Drug Discovery and Development
2017	University of Maryland School of Pharmacy AACP Teacher of the Year
2015	AACR Career Development Award (for Translational Breast Cancer Research)
2010	Summer Research Award, University of Louisiana at Lafayette
2008	Postdoctoral Fellowship, Proximagen, United Kingdom
2006	Graduate Dissertation Fellowship, Brown University
2001	Outstanding College Student of the Year, Anhui, China
2001	Excellent Student Scholarship of USTC, First Prize
2000	Excellent Student Scholarship of USTC, First Prize
1999	Excellent Student Scholarship of USTC, First Prize
1998	Japan Shi-Ye-Tong-Xun-Wang Fellowship
1997	Xu-Xin Fellowship, China

PROFESSIONAL MEMBERSHIPS

Society of Chinese Bioscientists in America (SCBA)

Sigma Xi (full member)

The American Chemical Society (ACS)

American Association of the Advancement of Science (AAAS)

American Association of Colleges of Pharmacy (AACP)

American Association of Pharmaceutical Scientists (AAPS)

American Association for Cancer Research (AACR)

EDITOR AND REVIEWER EXPERIENCE

Editorial Board:

Frontiers in Drug Discovery – Cardiovascular and Hematologic Drugs (2021 –)

Frontiers in Aging Neuroscience (2021 –)

Current Trends in Medicinal Chemistry

Reviewer for Journals:

ACS Applied Polymer Materials

ACS Chemical Biology

ACS Chemical Neuroscience

ACS Medicinal Chemistry Letters

Biochemistry

Bioorganic Chemistry

Bioorganic Medicinal Chemistry

Bioorganic Medicinal Chemistry Letters

Catalysis Communications

ChemComm

ChemMedChem

ChemistrySelect

Chemistry Letters

Expert Opinion on Investigational Drugs

European Journal of Medicinal Chemistry

Future Medicinal Chemistry

Journal of Combinatorial Chemistry

Journal of Enzyme Inhibition and Medicinal Chemistry

Journal of Infection in Developing Countries

Journal of Inorganic Biochemistry

Journal of Medicinal Chemistry

Journal of Natural Products

Letters in Organic Chemistry

MedChemComm

Medicinal Research Reviews Molecules

New Journal in Chemistry

NeuroReport

Organic Biomolecular Chemistry

Organic Chemistry Frontiers

Organic Letters

Organic Process Research & Development

Royal Society Open Science

RSC Advances

SynLett

Targeted Oncology

Tetrahedron Letters

Toxicology and Applied Pharmacology

Grants Review:

NIH/NIAID (January 2023, *scheduled*)

NIH ZRG1 IMST-K SBIR/STTR (May 2022)

NIH AIDC (12) SBIR: Nonviral Anti-infective Therapeutics Special Emphasis Panel (March 2022)

NIH ZRG1 AIDC-S (80) (March 2022)

NIH ZRG1 AIDC-S (80) (November 2021)

Swiss National Science Foundation (2021)

NIH BST-55: High-throughput screening (March 2019)

NIH BST-55: High-throughput screening (October 2018)

Great Lakes Fishery Commission

South Carolina NASA Space Grant

Outstanding Self-Financed International Graduate Student Fellowship (2013 – 2015)

INVITED SPEAKER AT SYMPOSIA; LECTURESHIP

1. Enhancers of CPA- and DOX-based chemotherapy. *Shanghai Institute of Technology*, *Nov 30*, **2022**
2. ALDH2 inhibitors for the treatment of AUDs. *NCATS*, *Aug 29*, **2022**
3. Enhancers of CPA- and DOX-based chemotherapy. *Towson University, Dec 9,* **2021**
4. BCL6 BTB Domain Inhibitors for Diffuse Large B-Cell Lymphomas. *SCBA Annual Meeting, December 12*, **2020**
5. Anti-Pseudomonal Agents by Targeting the Heme Uptake System. *Towson University, April 2,* **2020**
6. Small Molecule Therapeutics for DLBCL. *Loyola University in Chicago*, *March 19*, **2020**
7. Anti-Virulence by Targeting the *Pseudomonas aeruginosa* Heme Acquisition System. *Frontiers in Metals in Medicine Symposium, November 15,* **2019**
8. Therapeutics for Diffuse Large B-Cell Lymphomas. *Johns Hopkins University*, *November 11*, **2019**
9. Small Molecule Therapeutics for DLBCL. *Northwestern University*, *April 18*, **2018**
10. CAR Activators as a Sensitizer for Cyclophosphamide-Based Anti-Cancer Therapy. *The University of Tennessee Health Science Center*, *March 27*, **2018**
11. CAR Activators as a Sensitizer for Cyclophosphamide-Based Anti-Cancer Therapy. *Notre Dame of Maryland University*, *November 2*, **2017**
12. Wnt Signaling Inhibitors for the Treatment of Colorectal Cancer. *Nanjing Science and Technology University, July 3,* **2017**
13. Allosteric Inhibitors of Bacterial Heme Oxygenase as Novel Antimicrobial Agents. Shanghai University, *June 30,* **2017**
14. Wnt Signaling Inhibitors for the Treatment of Colorectal Cancer. *Jiaxing University, June 29,* **2017**
15. Wnt Signaling Inhibitors for the Treatment of Non-Alcoholic Fatty Liver Diseases (NAFLD). *Nanjing Normal University, June 19,* **2017**

16. Novel Wnt Inhibitors as Novel Treatment of Non-Alcoholic Fatty Liver Diseases (NAFLD). *University of Texas Austin*, *April 13*, **2017**
17. BCL6 BTB domain inhibitors for the treatment of DLBCL. *University of Wisconsin Milwaukee*, *November 18*, **2016**
18. Wnt Signaling Inhibitors for the Treatment of Type 2 Diabetes. *Brown University*, *October 7*, **2016**
19. BCL6 BTB Domain Inhibitors for DLBCL. *Virginia Commonwealth University*, *September 7*, **2016**
20. Small Molecule Inhibitors of the BCL6 BTB Domain as Potential Treatment for DLBCL. *CADD Symposium*, *Baltimore, MD*, *May 25*, **2016**.
21. Anti-Parasitic Agents by Targeting the Heme Transporters. *Texas Technology University*, *April 6*, **2016**.
22. Small Molecule Inhibitors of the BCL6 BTB Domain for Diffuse Large B-Cell Lymphomas. *University of Utah*, *March 24*, **2016**.
23. BCL6 BTB domain inhibitors for the treatment of DLBCL. *China Pharmaceutical University, June 9,* **2015**.
24. BCL6 BTB domain inhibitors for the treatment of DLBCL. *Nanjing University of Science and Technology, China, May 29,* **2015**.
25. Small molecule inhibitors of the BCL6 BTB domain for diffuse large B-cell lymphoma. *University of Maryland Baltimore County*, *MD*, *September 23*, **2014**.
26. Metabotropic Glutamate Receptor 5 Agonists as Drug Candidates for Traumatic Brain Injury. *CADD Symposium*, *MD*, *July 9*, **2012**.
27. Development of A Fluorometric Assay for Protein Serine/Threonine Phosphatase Calcineurin. *Xavier University of Louisiana*, *October 27*, **2011**.
28. Development of Novel Inhibitors of Neuronal Nitric Oxide Synthase for the Treatment of Neurodegenerative Diseases. *Symposium on Nitric Oxide and Other Gaseous Neurotransmitters*, *Toronto*, *Canada*, *May 27-28*, **2010**.

TEACHING ACTIVITIES

Course Taught at UMB

Year	Course #	Course Name	Credits	Role
2022	PHAR533	Med Chem 1	2	Course manager
	PHAR667	Org Synth Drug Design	1	Co-Course manager
	PHAR628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR600	Principles Drug Discov	1-3	Lecturer
	PHAR606	Experimental Success #1	1	Course manager
2021	PHAR608	Pharma Sci MS Lab Skills	1	Course manager
	PHAR533	Med Chem 1	2	Course manager
	PHAR628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR600	Principles Drug Discov	1-3	Lecturer

2020	PHAR608	Pharma Sci MS Lab	1	Course manager
	PHAR533	Med Chem 1	2	Course manager
	PHAR705	PSC Journal Club	1	Co-Course manager
	PHAR667	Org Synth Drug Design	1	Co-Course manager
	PHAR751	Drug Design	2	Lecturer
	PHMY551	Recent Adv Pharmacol	1	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR 600	Principles Drug Discov	1-3	Lecturer
2019	PHAR533	Med Chem 1	2	Course manager
	PHAR705	PSC Journal Club	1	Co-Course manager
	PHMY551	Recent Adv Pharmacol	1	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR 600	Principles Drug Discov	1-3	Lecturer
2018	PHAR533	Med Chem 1	2	Course manager
	PHAR705	PSC Journal Club	1	Co-Course manager
	PHAR667	Org Synth Drug Design	1	Co-Course manager
	PHAR539	Med Chem 2	2	SG proctor
	PHMY551	Recent Adv Pharmacol	1	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR 600	Principles Drug Discov	1-3	Lecturer
2017	PHAR533	Med Chem 1	2	Course manager
	PHAR705	PSC Journal Club	1	Co-Course manager
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHMY551/651	Recent Adv Pharmacol	1	Lecturer
	PHAR 600	Principles Drug Discov	1-3	Lecturer
2016	PHAR533	Med Chem 1	2	Course manager
	PHMY551/651	Recent Adv Pharmacol	1	Lecturer
	PHAR 600	Principles Drug Discov.	1-3	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR751	Drug Design	2	Lecturer
	REGS 614	Regulatory Science	3	Lecturer
2015	PHAR533	Med Chem 1	2	Course manager
	PHMY551/651	Recent Adv Pharmacol	1	Lecturer
	PHAR568	APS Debate		Mediator
	PHAR 600	Principles Drug Discov	1-3	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR667	Org Synth Drug Design	1	Co-Course manager
	REGS 614	Regulatory Science	3	Lecturer
2014	PHAR533	Med Chem 1	2	Course manager
	PHMY551/651	Recent Adv Pharmacol	1	Lecturer

	PHAR600	Principles Drug Discov	1-3	Lecturer
	PHAR628	Bioanal Pharmacol Methods	1-3	Lecturer
	PHAR751	Drug Design	2	Lecturer
2013	PHAR533	Med Chem 1	2	Course manager
	PHMY551/651	Recent Adv Pharmacol	1	Lecturer
	PHAR 600	Principles Drug Discov.	1-3	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
2012	PHAR533	Med Chem 1	2	Course manager
	PHAR 600	Principles Drug Discov	1-3	Lecturer
	PHAR 628	Bioanal Pharmacol Methods	1-3	Lecturer
2011	PHAR534	Med Chem 2	2	Lecturer
	PHMY551/651	Recent Adv Pharmacol	1-3	Lecturer

Course Taught in Previous Institutes

Year	Course Name	Credits	Role
University of Louisiana at Lafayette:			
2011	Organic Chemistry 1	3	Course manager
	Organic Chemistry Lab	1	Course manager
2010	Organic Chemistry 1	3	Course manager
	Organic Chemistry 2	3	Course manager
	Organic Chemistry Lab	1	Course manager
2009	Organic Chemistry 1	3	Course manager
	Organic Chemistry Lab	1	Course manager
Brown University:			
2005	Organic Chemistry Lab	1	Teaching Assistant
2004	Organic Chemistry Lab	1	Teaching Assistant
2003	Organic Chemistry Lab	1	Teaching Assistant
2002	Organic Chemistry Lab	1	Teaching Assistant
2001	General Chemistry Lab	1	Teaching Assistant

Fellows and Students Supervised

Postdoctoral Scholars

Yong Ai (2016 –)

Dongdong Liang (2015 – 2019)

Huimin Cheng (2015 – 2017)

Wei Yang (2014 – 2016)

Xinhua He (2012 – 2014)

Shilei Zhu (2013)

Hannah Mbatia (2011 – 2012)

Chuangyu Qi (2011 – 2012)

Graduate Students

Zijin Xu (2022 –)

Shuaiqian (Helen) Men (Rotation, Spring 2022)

Lena Grogan (Rotation, 2021 – 2022)

Aziza Frank (2021 – joint with the Wilks Lab, CBI trainee)

Nathaniel McClean (Rotation, Spring 2021)

Aziza Frank (Rotation, Fall 2020)

Christopher Goodis (Rotation, Spring 2020)

Matthew Hursey (Rotation, Fall 2018)

Benjamin Diethelm-Varela (2018 – 2021, CBI trainee, Master)

Asmita Adhikari (Rotation, Fall 2017)

Garrick Centola (2017 – 2022, Xue and Wilks Labs, CBI trainee)

Elizabeth Robinson (2016 – 2021, Xue and Wilks Labs, CBI trainee)

Geoffrey Heinzl (2011 – 2016, Xue and Wilks Labs, CBI trainee)

Kiwon Ok (Rotation, Spring 2016)

Chad Johnson (Rotation, Fall 2015)

Rachita Rai (2013 – 2015, graduated with a Master's degree)

Tao Liang (Rotation, Fall 2013)

PSC Master Students

Ayush Sinha (PSC Master Internship, 2022)

Mayur Umesh Shete (PSC Master Internship, 2022)

Ruchaa Charuhas Sapre (PSC Master Internship, 2022)

Gabriela Flores (2021)

Manali Kadam (2021)

Manali Nagarhalli (2020)

PharmD Research Students

Chiamaka Okereafor (2022)

Negar Hamidi (2021 – 2022)

Heng Ung (2020)

Aanye Gafrey (2020)

Lucia Hwang (2020 – 2022)
Ferideh Sistani-Khanaman (2018 – 2020)
Phuc Quang Tran (2017 – 2019)
Chun Yin Li (2017)
Nathan Shen (2017)
Ana Continho (2014 – 2018)
Nam Nguyen (2014 – 2019)
Tommy Lee (2015 – 2016)
Willy Lee (2015)
Sidick Jibril (2014 – 2015)
Priya Brunsdon (2015)
Kelly Murphy (2014)
Jung-Min Lee (2013 – 2014)

Undergraduate Students

UMB:
Faith (Malaika) Nyuawara (UMCP, Summer 2022)
Assefa Akinwole (UMBC, Summer 2019)
Keri McClelland (the Bryn Mawr School, Summer 2018)
Meredith Kuser (PSC Summer Intern Program 2018)
Alexandra Morris (PSC Summer Intern Program 2017)
Yue Yin (Binghamton University, Summer 2017)
Deanna Sersen (PSC Summer Intern Program 2016)
Nayara Cauneto (Federal University, Brazil, Summer 2015)
Wende Kyle (PSC Summer Intern Program 2014)
Tharcilla Aglio (Federal University, Brazil, Summer 2014)
Emily Sartain (PSC Summer Intern Program 2013)

ULL:
Charlie Roy (Summer 2010)
Venkatesh Thirumal (2009 – 2010)
Tom Nguyen (2009 – 2010)
Brad Landreneau (Spring 2010)

Northwestern:
George Michael (Spring 2009)
Julia Widom (Fall 2008)
William Lewis (Summer 2008)

Brown University: *Samuel Kim (Spring 2006)*
Clara Orber (Fall 2004)

Visiting Scholars *Dr. Wan Pang (2019 – 2020)*
Dr. Yu Li (2018 – 2019)
Dr. Jingming Zhao (2018)
Dr. Qianshou Zong (2016)
Dr. Chao Jiang (2014)
Dr. Shaymma Kassab (2014)
Dr. Xianyu Sun (2013)

PSC Ph.D. Comprehensive Exam and Thesis Committees Member

Samuel Krug (Thesis committee member)
Nathaniel McClean (Thesis committee member 2022)
Kyle Kihn (Thesis committee member)
Ritika Kurian (Thesis committee member)
Raquel Shortt (Thesis committee member)
Payal Chatterjee (Thesis committee member)
Sydney Stern (Thesis defense on 4-4-2022)
Brandon Drennen (Thesis defense on 10-31-2019, CBI trainee)
Obinna Obianom (Thesis defense on 5-18-2018)
Yewon Pak (Thesis defense on 5-22-2017, CBI trainee)
Joseph Thomas (Thesis defense on 11-15-2016)
Lijia Lee (Thesis defense on 10-2-2016)
Jeremy Yep (Thesis defense on 5-15-2014)
Diana Vivian (Thesis defense on 4-8-2014)

External Thesis Committee *Nopondo Ndoh Esemoto (UMBC, Thesis defense on 11-18-2022)*

Advisors for PSC Master Students *Gabriela Flores (2021)*
Manali Nagarhalli (2020)

Advisors for PharmD Students *7 Baltimore Students Class of 2026 (2022 –)*
20 Shady Grove Students Class of 2021 (2017 – 2021)
12 Shady Grove Students Class of 2017 (2014 – 2018)
10 Baltimore Students Class of 2019 (2013 – 2017)

Awards to Mentees

Garrick Centola: PSC Dean's Teaching Fellowship (Fall 2021)

Ferideh Sistani-Khanaman: Conrad L. Wich Prize: exceptional work in medicinal chemistry and pharmacology (2021)

Garrick Centola: PSC Science Fellowship Award (2020)

Garrick Centola: PSC Merit Award (2019)

Elizabeth Robinson: CBI Fellowship (2018 – 2020)

Priya Brunsdon: Medicinal Chemistry and Bioanalytical Chemistry Award, 2018

Ana Continho: Excellent Performance in Medicinal Chemistry, 2018

Jung-Min Lee: Conrad L. Wich Prize, 2016

Geoffrey Heinzl: AFPE Fellowship. 7/1/13 – 6/30/15

Geoffrey Heinzl: ACS Med Chem Fellowship. 7/1/14 – 6/30/15

SERVICE ACTIVITIES

National Organization

SCBA: DC-Baltimore Chapter, Treasurer (2020 – 2021)

AAPS: Drug Discovery and Development Interface (DDDI) Section Abstract Screening Committee (2015 – 2018)

UMB

UMB Faculty Senator (2017 – 2020)

UMB-SOP Committees

Faculty Affairs Committee (2020 – 2022)

Discipline and Grievance Committee (Ad Hoc, 21x) (2017 – 2022)

Student Affairs Committee (2015 – 2018, 2019 – 2021)

Curriculum Committee (2014 – 2015, 2022 –)

Curriculum Refinement Committee, Chemistry courses (2014)

Department of Pharmaceutical Service

PSC Instructor Searching Committee (2021)

PSC Graduate Steering Committee (2016 – 2020)

PSC Departmental Seminar Coordinator (2013 – 2020)

Director of PSC High Throughput Screening Core Facility (2016 –)

Other Service

Glorystar Children's Chorus, PSA President (2021 –)

Career Day Speaker, Beverly Farms ES, Potomac MD (2018)

Participation in the UMB-SOP PharmD Graduation Hooding Ceremony (2017)

UMB-SOP Rho Chi Research Round-Table (2016)

Participation in the UMB-SOP White Coat Ceremony (2015)

Career Day Speaker, the Beverly Farms ES, Potomac (2015)

UMB-SOP PharmD Research Round-Table, Baltimore (2014)

UMB-SOP PharmD Research Round-Table, Shady Grove (2014)

PSC PhD Recruitment Trip, Temple University (2013)

PSC PhD Recruitment Trip, UMBC (2013)

PSC PhD Program Recruitment Trip, Xavier University (2012)

UMB Graduate Research Day Poster Judge (2012)

PharmD Interview (2011 – 2018, eight times)

SCHOLARLY ACTIVITIES

Publications in Refereed Journals (* = Corresponding Author)

1. Ruan J, Liang D, Yan W, Zhong Y, Talley DC, Rai G, Tao D, LeClair CA, Simeonov A, Zhang Y, Chen F, Quinney NL, Boyles SE, Cholon DM, Gentzsch M, Henderson MJ, Xue F, Fang S. 2022 A small-molecule inhibitor and degrader of the RNF5 ubiquitin ligase. ***Mol. Biol. Cell*** 33(3):ar120. PMID: 36074076
2. Zhang J, Li Q, Kawashima SA, Nasr M, Xue F, Zhao R. **2022.** Improving drug sensitivity of HIV-1 protease inhibitors by restriction of cellular efflux system in a fission yeast model. ***Pathogen*** 11(7):804. PMID: 35890048
3. Stern S, Liang D, Li L, Kurian R, Lynch C, Srilatha S, Heyward S, Zhang J, Kareen KA, Chun Y W, Huang R, Xia M, Charles C, Xue F, Wang H. **2022.** Targeting CAR-Nrf2 improves cyclophosphamide bioactivation while reducing doxorubicin-induced cardiotoxicity in triple-negative breast cancer treatment. ***JCI Insight*** 7(12):e153868. PMID: 35579950
4. Ai Y, Sakamuru S, Imler G, Xia M, Xue F. **2022.** Wnt/*β*-catenin signaling inhibitors with improved aqueous solubility and anti-leukemia activity by disrupting molecular planarity. ***Bioorg. Med. Chem.*** 69:116890. PMID: 35777269
5. Frank A, Hamidi N, Xue F. **2022.** Regioselective alkylation of 2,4-dihydroxybenzyaldehyde and 2,4-dihydroxyacetophenones. ***Tetrahedron Lett.*** 95:153755. PMID: 35495552
6. Robinson E, Frankenberg-Dinkel N, Xue F, Wilks A. **2021**. Recombinant production of biliverdin IXb and d isomers in the T7 promoter compatible Escherichia coli Nissle (EcN(T7)). ***Front. Microbiol.*** 12:787609. PMID: 34956154
7. Cai Y, Poli ANR, Vadrevu S, Gyampoh K, Hart C, Ross B, Fair M, Xue F, Salvino JM, Montaner LJ. **2021**. BCL6 BTB-specific inhibitor reversely represses T-cell activation, Tfh cells differentiation, and germinal center reaction in vivo. ***Eur. J. Immunol.*** 51(10):2441-2451. PMID: 34287839
8. Robinson E, Wilks A, Xue F. **2021**. Repurposing acitretin as an antipseudomonal agent targeting the *Pseudomonas aeruginosa* iron-regulated heme oxygenase. ***Biochemistry*** 60(9):689-698. PMID: 33621054

9. Ai Y, Hwang L, MacKerell Jr. AD, Melnick A, Xue F. **2021**. Progress towards B-cell lymphoma 6 BTB domain inhibitors for the treatment of diffuse large B-cell lymphoma and beyond. ***J. Med. Chem.*** 64(8):4333-4358. PMID: 33844535

10. Ruan J, Liang D, Zhong Y, Talley DC, Yan W, Gentzsch M, Rai G, Tao D, Zhang Y, Chen F, Henderson MJ, Xue F, Fang S. **2021**. A small molecule hijacks ERAD pathway to degrade RNF5 and improves ΔF508CFTR stability and trafficking. ***J. Biol. Chem.*** submitted

11. Diethelm-Varela B, Kumar A, Lynch C, Imler G, Deschamps J, Li Y, Xia M, MacKerell Jr., AD, Xue F. **2021**. Stereoisomerization of 6-(4-chlorophenyl)imidazo[2,1-*b*][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO). ***Tetrahedron*** 79:131886. (Cover Article)

12. Li S, Zhao J, Huang R, Travers J, Klumpp-Thomas C, Yu W, MacKerell A, Xue F, Sipes NS, Hsieh J, Ryan K, Simeonov A, Santillo MF, Xia M, **2021.** Profiling the Tox21 chemical collection for acetylcholinesterase inhibition. ***Environ. Health Perspect.*** 129(4):047008. PMID: 33844597

13. Centola G, Xue F, Wilks A. **2020**. Metallotherapeutics Development in the Age of Iron-Clad Bacteria. ***Metallomics*** 12:1863-1877. PMID: 33242314

14. Centola G, Deredge DJ, Hom K, Dent AT, Xue F,* Wilks A. **2020**. Gallium (III) salophen as a dual inhibitor of *Pseudomonas aeruginosa* heme sensing and iron acquisition. ***ACS Infect. Dis.*** 6(8): 2073-2085. PMID: 32551497

15. Thomas JM, Wang X, Gong G, Li T, Dai B, Sun X, Nucifora LG, Nucifora Jr. FC, Liu Z, Xue F, Liu C, Ross CA, Smith W. **2020**. GTP-binding inhibitors increase LRRK2-linked ubiquitination and inclusions. ***J. Cell. Physiol.*** 235(10): 7309-7320. PMID: 32180220

16. Cai Y, Watkins MA, Xue F, Ai Y, Cheng HM, Midkiff CC, Wang X, Alvarez X, Salvino JM, Veazey RS, Montaner L. **2020**. BCL6 BTB-specific inhibition via FX1 treatment reduces Tfh cells & reverses lymphoid follicle hyperplasia in indian rhesus macaque (macaca mulatta). ***J. Med. Primatol.*** 49(1): 26-33. PMID: 31571234

17. Yang W, Li Y, Ai Y, Obianom ON, Guo D, Yang H, Sakamuru S, Xia M, Shu Y, Xue F.* **2019**. "Pyrazole-4-carboxamide (YW2065): A therapeutic candidate for colorectal cancer via dual activities of Wnt/β-catenin signaling inhibition and AMP-activated protein kinase (AMPK) activation" ***J. Med. Chem.*** 62(24):11151-11164. PMID: 31769984

18. Liang D, Li L, Lynch C, Mackowiak B, Hedrich WD, Ai Y, Yin Y, Heyward S, Xia M, Wang H, Xue F.* **2019**. Human constitutive androstane receptor agonist DL5016: a novel sensitizer for cyclophosphamide-based chemotherapies. ***Eur. J. Med. Chem.*** 179:84-99. PMID: 31247375

19. Liang D, Li L, Lynch C, Xia M, Wang H, Xue F.* **2019.** DL5050: a selective agonist for the human constitutive androstane receptor. ***ACS Med. Chem. Lett.*** 10(7):1039-1044. PMID: 31312405.

20. Diethelm-Varela B, Ai Y, Liang D, Xue F.* **2019.** Nitrogen mustards as anticancer chemotherapies: historic perspective, current developments, and future trends. ***Curr. Topics Med. Chem.*** 19(9): 691-712.

21. Zhao J, Liang D, Robinson E, Xue F.* **2019.** The effects of novel heme oxygenase inhibitors on the growth of *Pseudomonas aeruginosa*. ***Microbial Pathogenesis*** 129:64-67.

22. Ai Y, Obianom ON, Kuser M, Li Y, Shu Y, Xue F.* **2019.** Enhanced tumor-selectivity of 5-fluorouracil using a reactive oxygen species-activated prodrug approach. ***ACS Med. Chem. Lett.*** 10:127-131. PMID: 30655959

23. Cai Y, Abdel-Mohsen M, Tomescu C, Xue F, Wu G, Howell BJ, Ai Y, Sun J, Azzoni L, Coz CL, Romberg N, Montaner LJ. **2019.** BCL6 inhibitor-mediated downregulation of pSAMHD1 and T cell

activation are negatively associated with HIV infection and reactivation. ***J. Virol.*** 93(2):e01073/1-15.

24. Obianom ON, Ai Y, Li Y, Yang W, Guo D, Yang H, Sakamuru S, Xia M, Xue F,* Shu Y. **2019.** Triazole-based inhibitors of the Wnt/*β*-catenin signaling pathway improves glucose and lipid metabolism in diet-induced obese mice. ***J. Med. Chem.*** 62(2):724-741. PMID: 30605343
25. Heinzl GA, Huang W, **Xue F,** Moenne-Loccoz P, Wilks A. "The Asp99-Arg188 Salt Bridge of the Pseudomonas aeruginosa HemO is Critical in Allowing Conformational Flexibility During" *J. Biol. Inorg. Chem.* **2018**, *23*, 1057-1070.
26. Metry, M.; Felton, J.; Cheng, K.; Xu, S.; Ai, Y.; Xue, F.; Raufman, J.; Polli, J. "Attenuated Accumulation of Novel Fluorine (19F)-Labeled Bile Acid Analogues in Gallbladders of Fibroblast Growth Factor-15 (FGF15)-Deficient Mice" *Mol. Pharm*. **2018**, *15*, 4827-4834.
27. Zhao, S.; Yasir, M.; Zeng, W.; Cheng, L.; Zhou, X.; **Xue, F.;*** Jiang. C. "Palladium-Catalyzed C2-Selective Alkynylation of Indoles with Bromoalkynes" *Tetrahedron Lett.,* Submitted
28. Cheng, H.; Linhares, B. M.; Yu, W.; Cardenas, M. G.; Ai, Y.; Jiang, W.; Melnick, A.; MacKerell, A.; Cierpicki, T.; **Xue, F.*** "Thiourea-Based Inhibitors of the BCL6 BTB Domain via NMR-Based Fragment Screening and Computer-Aided Drug Design" *J. Med. Chem.* **2018,** *61*, 7573-7588.
29. Liang, D.; Robinson, E.; Hom, K.; Yu, W.; Nguyen, N.; Li, Y.; Zong, Q.; Wilks, A. **Xue, F.*** "Structure-based design and biological evaluation of inhibitors of the *Pseudomonas aeruginosa* heme oxygenase (*pa*-HemO)" *Bioorg. Med. Chem. Lett.* **2018,** *28*, 1024-1029.
30. Gao, Y.; Zhu, W.; Yin, L.; Dong, B.; Fu, J.; Ye, Z.; **Xue, F.***; Jiang, C. "Palladim-Catalyzed Direct C2-Arylation of Free (N-H) Indoles via Norbornene-Mediated Regioselective C-H Activation" *Tetrahedron Lett.* **2017**, *58*, 2213-2216.
31. Liang, D.; Sersen, D.; Deschamps, J. R.; Imler, G. H.; Jiang, C.; **Xue, F.*** "One-Pot Sequential Reaction to 11-Substituted-Phenanthridinones from *N*–Methoxybenzamides" *Org. Biomol. Chem.* **2017**, *15*, 4390-4398.
32. Deb, D.; Rajaram, S.; Larsen, J. E.; Dospoy, P. P.; Marullo, R.; Li, L. S.; Avila, K.; **Xue, F.**; Cerchietti, L.; Minna, J. D.; Altschuler, S. J.; Wu, L. F. "A Novel Combination Therapy Targeting BCL6 and Phospho-STAT3 Defeats Intra-tumor Heterogeneity in a Subset of Non-Small Cell Lung Cancer" *Cancer Res.* **2017**, *77*, 3070-3081.
33. Madapura, H. S.; Nagy, N.; Njvari, D.; Kallas, T.; Krohnke, M.; Amu, S.; Bjorkholm, M.; Stenke, L.; Mandal, P. K.; McMurray, J. S.; Keszei, M.; Westerberg, L. S.; Cheng, H.; **Xue, F.**; Klein, G.; Klein, E.; Salamon, D. "Interferon γ is a STAT1-Dependent Direct Inducer of BCL6 Expression in Imatinib Treated Chronic Myeloid Leukemia Cells" *Oncogene*, **2017**, *36*, 4619-4628.
34. Liang, D.; Yu, W.; Nguyen, N.; Deschamps, J. R.; Imler, G. H.; Li, Y.; MacKerell, Jr., A. D.; **Xue, F.*** "Iodobenzene-Catalyzed Synthesis of Phenanthridiones via Oxidative C-H Amidation" *J. Org. Chem.* **2017**, *82*, 3589-3596.
35. Obianom, O. N.; Coutinho, A. L.; Yang, W.; Yang, H.; **Xue, F.***; Shu, Y. "Incorporation of a Biguanide Scaffold Enhances Drug Uptake by Organic Cation Transporter 1 and 2" *Mol. Pharm*. **2017**, *14*, 2726-2739.
36. Thomas, J. M.; Li, T.; Yang, W.; **Xue, F.**; Fishman, P. S.; Smith, W. "68 and FX2149 Attenuate Mutant LRRK2-R1441C-Induced Neural Transport Impairment" *Front. Aging Neurosci*., **2017**, *8*, Article 337(1-11).
37. Cardenas M. G.; Yu, **Xue, F.*;** MacKerell, A. D.; Melnick, M. M. "Therapeutic Targeting of GCB- and ABC-DLBCLs by Rationally Designed BCL6 Inhibitors" *Clin. Cancer Res.* **2017,** *23*, 885-893.

38. Yang, C.; Cheng, G.; Huang, B.; **Xue, F.*;** Jiang, C. "Metal-free Regioselective Construction of Indolin-3-ones via Hypervalent Iodine Oxidation of *N*-Substituted Indoles" *RSC Adv.* **2016**, 6, 87134-87141.

39. Heinzl, G. A.; Huang, W.; Yu, W.; Giardina, B. J.; Zhou, Y.; MacKerell, A. D.; Wilks, A.; **Xue, F.*** "Iminoguanidines as Allosteric Inhibitors of the Iron-Regulated Heme Oxygenase (HemO) of *Pseudomonas aeruginosa*" *J. Med. Chem.* **2016**, *59*, 6929-6942.

40. Cardenas M. G.; Yu, Wendy Beguelin, W.; Teater, M. R.; Geng, H.; Goldstein, R. L.; Oswald, E.; Katerina Hatzi1, K.; Yang, S.; Cohen, J.; Shaknovich, R.; Vanommeslaeghe, K.; Cheng, H.; Liang, D.; Cho, H. J.; Abbott, J.; Tam, W.; Leonard, J. P.; Cerchietti, L.; Cierpicki, T.; **Xue, F.***; MacKerell, A. D.; Melnick, M. M. "Therapeutic Targeting of GCB- and ABC-DLBCLs by Rationally Designed BCL6 Inhibitors" *J. Clin. Invest.* **2016,** *126*, 3351-3362. (**cover article**)

41. Cheng, X.; Chen. Z.; Gao, Y.; **Xue, F.***; Jiang, C. "Aminoquinoline-Assisted Vinylic C-H Arylation of Unsubstituted Acrylamide for the Selective Synthesis of Z Olefins" *Org. Biomol. Chem.* **2016**, *14*, 3298-3306. (**Highlighted by Synfacts, issue 05/2016**)

42. Yang, W.; Coutinho, A.; L.; Abdel-Hafez, A. A.; Jiang, C.; **Xue, F.*** "Ligand-Free Copper-Mediated *N*-Arylation of Spirocyclic Keto-Lactams" *Tetrahedron Lett.* **2015**, *56,* 5599-5603.

43. Zhao, J.; Chen. X.; Le, J.; Yang, W.; **Xue, F.***; Zhang, X.; Jiang, C. "Cu-Mediated Direct Regioselective C-2 Chlorination of Indoles" *Org. Biomol. Chem.* **2015**, *13(34)*, 9000-9004.

44. Holden, J. K.; Dejam, D.; Lewis M. C.; Huang, H.; Kang, S.; Jing, Q.; **Xue, F.**; Silverman, R. B.; Poulos, T. L. "Inhibitor Bound Crystal Structures of Bacterial Nitric Oxide Synthase" *Biochemistry* **2015**, *49*, 4075-4082.

45. Yang, W.; Sun, X.; Yu, W.; Rai, R.; Deschamps, J. R.; Mitchell, L. A.; Jiang, C.; MacKerell, Jr., A. D.; **Xue, F.*** "Facile Synthesis of Spirocyclic Lactams from β-Keto Carboxylic Acids" *Org. Lett.* **2015**, *17*, 3070-3073.

46. Lakkaraju, S. K.; Mbatia, H.; Hanscom, M.; Zhao, Z.; Wu, J.; Stoica, B.; MacKerell, Jr., A. D.; Faden, A. I.; **Xue, F.*** "Cyclopropyl-Containing Positive Allosteric Modulators of Metabotropic Glutamate Receptor Subtype 5" *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2275-2279.

47. He, X.; Lakkaraju, S. K.; Hanscom, M.; Zhao, Z.; Wu, J.; Stoica, B.; MacKerell, Jr., A. D.; Faden, A. I.; **Xue, F.*** "Acyl-2-Aminobenzimidazoles: A Novel Class of Neuroprotective Agents Targeting mGluR5" *Bioorg. Med. Chem.* **2015**, *23*, 2211-2220.

48. Li, T.; He. X.; Thomas, J. M.; Yang, D.; Zhong, S.; **Xue, F.***; Smith, W. "A Novel GTP-Binding Inhibitor, FX2149, Attenuates LRRK2 Toxicity in Parkinson's Disease Models" *PLOS One* **2015**, *10*: e0122461.

49. He, X.; Aglio, T.; Deschamps, J. R.; Rai, R.; **Xue, F.*** "Synthesis of 1,2-Dihydro-2-Oxo-4-Quinolinyl Phosphates from 2-Acyl-Benzoic Acids" *Tetrahedron Lett.* **2015**, *56*, 1441-1444.

50. He, X.; Kassab, S. E.; Heinzl, G.; **Xue, F.*** "Base-Catalyzed One-Step Synthesis of 5,7-Disubstituted-1,2,4-Triazolo[1,5-*a*]pyrimidines" *Tetrahedron Lett.* **2015**, *56*, 1034-1037.

51. Holden, J.; Kang, S.; Hollingsworth, S.; Li, H.; Lim, N.; Chen, S.; Huang, H.; **Xue, F.**; Tang, W.; Silverman, R.; Poulos, T. "Structure-Based Design of Bacterial Nitric Oxide Synthase Inhibitors" *J. Med. Chem.* **2015**, *58*, 994-1004.

52. Loane, D. J.; Stoica, B. A.; Tchantchou, F.; Kumar, A.; Barrett, J. P.; Akintola, T.; **Xue, F.**; Conn, P. J.; Faden, A. I. "Novel mGluR5 Positive Allosteric Modulator Improves Functional Recovery, Attenuates Neurodegeneration, and Alters Microglial Polarization after Experimental Traumatic Brain

Injury" *Neurotherapeutic*s, **2014**, *11*, 857-869.

53. Li, T.; Yang, D.; Zhong, S.; Thomas, J. M.; **Xue, F.**; Liu, J.; Kong, L.; Voulalas, P.; Hassan, H. E.; Park, J. S.; MacKerell, A. D.; Smith, W. W. "Novel LRRK2 GTP-binding Inhibitors Reduced Degeneration in Parkinson's Disease Cell and Mouse Models" *Hum. Mol. Genet.* **2014**, 23, 6212-6222.
54. **Xue, F.***; Stoica, B. A.; Hanscom, M.; Kabadi, S. V.; Faden, A. I. "Positive Allosteric Modulators (PAMs) of Metabotropic Glutamate Receptor 5 (mGluR5) Attenuate Microglial Activation" *CNS & Neurol. Disord. Drug Targets* **2014**, *13*, 558-566.
55. Kao, J. P. Y.; Muralidharan, S.; Zavalij, P. Y.; Fletcher, S.; **Xue, F.**; Rosen, G. M. "Baeyer-Villiger Rearrangement of a Substituted Pyrrole by Oxone" *Tetrahedron Lett.* **2014**, *55*, 3111-3113.
56. He, X.; **Xue, F.*** "Transition-Metal-Free Synthesis of (*Z*)-3-Ylidenephthalides from 2-Acyl-Benzoic Acids" *Tetrahedron Lett.* **2014**, *55*, 1956-1958.
57. Sun, X.; Rai, R.; MacKerell, Jr., A. D.; Faden, A. I.; **Xue, F.*** "Facile One-Step Synthesis of 2,5-Diketopiperazines" *Tetrahedron Lett.* **2014**, *55*, 1905-1908.
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Patents

1. **Xue F**. **2022** "Pyrazinamide-mimicking small molecules as treatment for tuberculosis" Provisional Filed on Dec 1.
2. **Xue F,** Wilks A. **2022** "Gallium-Salophen Antimicrobial Compounds and Methods of Use Thereof" Provisional Filed on Dec 1.
3. Wang J, **Xue F. 2022** "Composition and methods for treating proteotoxicity-associated diseases" Patent application (PCT/US22/075352), filed on Aug 23.
4. Zhou Q, **Xue F**. **2022** "Discovery of a novel endothelial lipase inhibitor FX5153" Provisional Filed on May 11.
5. Wang H, **Xue F**, Li L. **2021** "Car and Nrf2 dual activator agents for cyclophosphamide-based and doxorubicin-based treatments of cancer" Invention Disclosure Filed on March 3.
6. **Xue F,** Ai Y, Shu Y. **2021** "Dual WNT signaling pathway inhibitors and AMPK activators for treatments of diseases" Invention Disclosure Filed on June 1.
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19. Silverman RB, **Xue F. 2015** "Aminopyridine Dimer Compounds, Compositions and Related Methods for Neuronal Nitric Oxide Synthase Inhibition." Pat. # US 8,932,842 B2, issued date: *Jan 13*.

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Conference Presentations/Abstracts

1. Xue, F. **2022** "Pseudomonas aeruginosa heme sensing and utilization inhibitors targeting HasAp and HemO". Gordon Research Conferences: *Tetrapyrroles, Newport RI, July 17-22*.

2. Ai, Y, Xue F. **2020** "YW2065 with dual activities of Wnt/β-catenin inhibition and AMPK activation for colorectal cancer" *ACS National Meeting*, *San Francisco (virtual meeting)*, *CA*, *Aug. 17-20*.

3. Xue F. **2020** "Developing DL5055 as an enhancer for cyclophosphamide-based chemotherapeutics" *ACS National Meeting*, *San Francisco (virtual meeting)*, *CA*, *Aug. 17-20*.

4. Diethelm-Varela B, Xue F. **2020** "Stereoisomerization of the human CAR activator CITCO complicates its use as a reference ligand" *ACS National Meeting*, *San Francisco (virtual meeting)*, *CA*, *Aug. 17-20*.

5. Robinson E, Wilks A, Xue F. **2020** "Discovery and characterization of retinoic acid derivatives as inhibitors against *Pseudomonas aeruginosa* heme oxygenase" *ACS National Meeting*, *San Francisco (virtual meeting)*, *CA*, *Aug. 17-20*.

6. Centola G, Deredge DJ, Hom K, Dent AT, Ai Y, Wilks A, Xue F. **2020** "Development of metallotherapeutics targeting *Pseudomonas aeruginosa* heme sensing and iron acquisition pathways" *ACS National Meeting*, *San Francisco (virtual meeting)*, *CA*, *Aug. 17-20*.

7. Wang Y, Ai Y, Xue F, Hummon A. **2020** "MALD-MSI Evaluation of Penetration of Different Pyrazole-based Compounds into Multicellular Tumor Spheroids" ASMS.

8. Sistani-Khanaman F, Ai Y, Shapiro P, Xue F. **2020** "Enhancing tumor selectivity of 6-mercaptopurine using a reactive oxygen species-activated prodrug approach" APhA2020.

9. Vetrie D, Bugler J, Liu W, Michell R, Kinstrie R, Xue F, Melnick A, Copland M, Scott M. **2020** "Dual EZH2 and BCL6 inhibition targets CML stem cells via a gene network co-regulated with c-Myc" EHA-3000.

10. Robinson, E., Wilks, A.; Xue, F. "Identification and characterization of inhibitors of the Pseudomonas aeruginosa heme oxygenase". Gordon Research Conferences: Tetrapyrroles, Spain, **2019**.

11. Centola, G.; Xue, F. Wilks A. "Heme Sensing Inhibitors in Pseudomonas aeruginosa with Metallosalophen Complexes". Gordon Research Conferences: Tetrapyrroles, Spain, **2019**.

12. Ai, Y.; Obianom, O.; Shu, Y.; **Xue, F.**; "Reactive Oxygen Species (ROS) Triggered 5-Fluorouracil Prodrugs" *255th ACS National Meeting*, *New Orleans*, *LA*, *Mar. 18-22*, **2018.**

13. Liang, D.; Li, L.; Wang, H.; **Xue, F.** "Human CAR Activators as Sensitizers of Cyclophosphamide-Based Treatment for Lymphomas" *255th ACS National Meeting*, *New Orleans*, *LA*, *Mar. 18-22*, **2018.**

14. Centola, G.; Jiang, W.; Hom, K.; Wilks, A.; **Xue, F.** "*Identification of Inhibitors of the Pseudomonas aeruginosa* HasAp/HasR Protein-Protein Interaction" *255th ACS National Meeting*, *New Orleans*, *LA*, *Mar. 18-22*, **2018.**

15. Robinson, E.; Liang, D.; Mourino, S.; **Xue, F.**; Wilks, A. "High Throughput *in vivo* Screening Assay for Novel Inhibitors of Extracellular Heme Sensing and Utilization in *Pseudomonas aeruginosa*" *255th ACS National Meeting*, *New Orleans*, *LA*, *Mar. 18-22*, **2018.**

16. Cai, Y.; Abdel-Mohsen, M.; Tomescu, C.; Fair, M.; Azzoni, L.; Papasawas, E.; **Xue, F.**; Sun, J.; Romberg, N. D.; Coz, C. L.; Montaner, L. J. "Bcl6 inhibition represses THF/non-THF HIV infection and T-cell/myeloid activation" *Conference on Retroviruses and Opportunistic Infections*, *Boston*, *Massachusetts*, *Mar. 4-7*, **2018**.

17. Gresely, B. P.; **Xue, F.**; Ai, Y.; Barasoain, I.; Perez, F.; Cerchetti, L. "Development of a Novel Class of Microtubule Destabilizing Agents with Selectivity Against Diffuse Large B-Cell Lymphoma (DLBCL) with B-Cell Receptor (BCR) Activation" *The 59th ASH Annual Meeting and Exposition*, *Atlanta*, Georgia , *Dec. 9-12*, **2017.**

18. Cai, Y.; Tomescu, C.; Abdel-Mohsen, M.; Fair, M.; Azzoni, L.; Papasavvas, E.; **Xue, F.;** Sun, J.; Romberg, N. D.; Coz, C. L.; Montaner, L. J. "Bcl6 inhibition represses HIV infection ex vivo by suppression of immune activation: Implication for viral clearance in the secondary lymphoid tissue of HIV-infected patients undergoing ART treatment" *The 50th SLB Annual Meeting, Vancouver, Canada, Oct 4-7,* **2017**.

19. Robinson, E.; Heinzl, G.; Liang, D.; Hom, K.; Wilks, A.; **Xue, F.** "Inhibition of the *Pseudomonas aeruginosa* heme oxygenase" *254th ACS National Meeting*, *Washington*, *DC*, *Aug. 20-24*, **2017.**

20. Nguyen, N.; Liang, D.; Yu, W.; Deschamps, J. R.; Imler, G. H.; Li, Y.; MacKerell, Jr., A. D.; **Xue, F.** "Iodobenzene-Catalyzed Synthesis of Phenanthridiones via Oxidative C-H Amidation" *254th ACS National Meeting*, *Washington*, *DC*, *Aug. 20-24*, **2017.**

21. Coutinho, A. L.; Obianom, O. N.; Yang, W.; Shu, Y.; **Xue, F.** "Biguanides Enhance Drug Uptake by Organic Cation Transporters" *254th ACS National Meeting*, *Washington*, *DC*, *Aug. 20-24*, **2017.**

22. Ai, Y.; Yang, W.; Li, Y.; Shu, Y.; **Xue, F.** "Wnt/β-catenin Inhibitors for the Treatment of Colorectal Cancer" *254th ACS National Meeting*, *Washington*, *DC*, *Aug. 20-24*, **2017.**

23. Jiang, C.; Yang, C.; Cheng, G.; Huang, B.; **Xue, F.** "Metal-Free Regioselective Construction of Indolin-3-ones via Hypervalent Iodine Oxidation of *N*-Substituted Indoles" *254th ACS National Meeting*, *Washington*, *DC*, *Aug. 20-24*, **2017.**

24. **Xue, F.** "Anti-Parasitics by Targeting the Heme Transporters LHR1" *Gordon Research Conferences*: *Tetrapyrroles*, *Newport RI*, *July 17-21*, **2016.**

25. **Xue, F.** "Benzimidoguanidines as Allosteric Inhibitors of the Iron-Regulated Heme Oxygenase (HemO) of Pseudomonas aeruginosa" *Gordon Research Conferences*: *Tetrapyrroles*, *Andover NH*, *June 26 – July 1*, **2016.**

26. Johnson, C.; Liang, D.; Yuan, X.; Hamza, I.; **Xue, F.** "Antiparasitic agents targeting LHR1"*252nd ACS National Meeting*, *Philadelphia*, *PA*, *Aug. 21-25*, **2016.**

27. Cheng, H.; **Xue, F.** "BCL6 BTB Domain Inhibitors for DLBCLs"*252nd ACS National Meeting*, *Philadelphia*, *PA*, *Aug. 21-25*, **2016.**

28. Heinzl, G.; Wilks, A.; **Xue, F.**; "HemO inhibitors as antivirulence" *Gordon Research Conferences*, *August 1-5*, **2015**.

29. Kassab, S. E.; Yu, W.; MacKerell, A.; **Xue, F**. "Small Molecule Inhibitors of the BCL6 BTB Domain for DLBCLs" *248th ACS National Meeting*, *San Francisco*, *CA*, *August. 10-14*, **2014.**

30. Rai, R.; **Xue, F.**; MacKerell, A.; Lakkaraju, S. K. "Synthesis and Evaluation of Protein Tyrosine Phosphatase Inhibitors by Targeting a Novel Allosteric Site" *248th ACS National Meeting*, *San Francisco*, *CA*, *August. 10-14*, **2014.**

31. Cardenas, M.; Yu, W.; Zhu, S.; Cerchietti, L.; Melnick, A.; MacKerell, A. D.; **Xue, F.** "Targeting B-Cell Lymphoma 6 (BCL6) for the Treatment of Diffuse Large B-Cell Lymphomas (DLBCLs)" *246th ACS National Meeting*, *Indianapolis*, *IN*, *Sept. 8-12*, **2013.**

32. He, X.; Hanscom, M.; Stoica, B.; MacKerell, A. D.; Faden, A. I.; **Xue, F.** "Centrally Active Positive Allosteric Modulators (PAMs) of Metabotropic Glutamate Receptor 5 (mGluR5) for Traumatic Brain Injury (TBI)" *246th ACS National Meeting*, *Indianapolis*, *IN*, *Sept. 8-12*, **2013.**

33. Heinzl, G.; Hom, K.; Lopez, P.; MacKerell, A. D.; Wilks, A.; **Xue, F.** "Inhibitors of Iron-regulated heme oxygenase (HemO) of Pseudomonas aeruginosa as Novel Antivirulant Agents" *245th ACS National Meeting*, *New Orleans*, *LA*, *April. 7-11*, **2013.**

34. **Xue, F.**; Mbatia, H.; MacKerell, A. D., Jr.; "Highly-Efficient Method to Isatinylidenerhodanine Formation: Synthesis and Mechanistic Studies "*244th ACS National Meeting*, *Philadelphia*, *PA*, *Aug. 19-23*, **2012**.

35. Nagarajan, S.; **Xue, F.**; MacKerell, A. D., Jr.; "Charge Dependent Behavior of Substrate Arginine in the Arginase I Environment "*244th ACS National Meeting*, *Philadelphia*, *PA*, *Aug. 19-23*, **2012**.

36. **Xue, F.**; "Positive Allosteric Modulators of the Metabotropic Glutamic Receptor 5 for Traumatic Brain Injury" *NIH GM Workshop*, *Dallas*, *May 6-9*, **2012**.

37. **Xue, F.**; "Development of Novel Inhibitors of Neuronal Nitric Oxide Synthase for the Treatment of Neurodegenerative Diseases." *Symposium on Nitric Oxide and Other Gaseous Neurotransmitters*, *Toronto*, *Canada*, *May 27-28*, **2010** (invited talk).

38. **Xue, F.**; "Neuronal Nitric Oxide Synthase Inhibitors as Drug Candidates for Neurodegenerative Diseases." *Southern Louisiana Symposium of Chemistry*, *Lake Charles*, *LA*, *Sept 25*, **2009**.
39. **Xue, F.**; Seto, C. T. "Development of Fluorogenic Substrate for Serine/Threonine Phosphatases." *Gordon Research Conferences*, **2007**.
40. **Xue, F.**; Seto, C. T. "Fluorescent Probes to Study Serine/Threonine Phosphatases." *232th ACS National Meeting*, *San Francisco*, *CA*, *Sept. 10-14*, **2006**.
41. **Xue, F.**; Seto, C. T. "Macrocyclic Inhibitors of the Serine Protease Plasmin: Development and Biological Activity." *231th ACS National Meeting*, *Atlanta*, *GA*, *Mar. 25-30*, **2006**.
42. **Xue, F.** Seto, C. T. "Combinatorial Library of Inhibitors for Serine Protease Plasmin: Binding Specificity at S3 and S3' Subsites." *230th ACS National Meeting*, *Washington*, *DC*, *Aug. 28-Sept. 1*, **2005**.
43. **Xue, F.**; Seto, C. T. "4-Heterocyclohexanone-Based Inhibitors of Serine Protease Plasmin." *229th ACS National Meeting*, *San Diego*, *CA*, *March 13-17*, **2005**.

GRANTS

Grants to PSC HTS Lab

1. ICTR Sub Xue (PI) 05/01/2020 – 04/30/2021
   The University of Maryland Baltimore County $15,000
   High-throughput screen to identify novel selective regulators of mutant p53 in ovarian cancer cells
   The goal of our research is to identify small molecule hits as selective regulators of mutant p53.

Active Grants to Xue Lab

1. NEXUS Sub Xue (PI) 12/1/2022 – 08/31/2023
   Johns Hopkins University $30,000
   Novel Wnt Signaling Pathway Inhibitors for the Treatment of Colorectal Cancer.
   The goal of our research is to synthesize and test Wnt signaling inhibitor YA6060 as potential therapeutic candidates for the treatment of colorectal cancer.
2. VA Merit Award (BX004264) Contract 1/1/2022 – 9/30/2022
   Project Title: "Improving the membrane permeability of LIPG inhibitors"
   $50,000 direct cost to the Xue Lab
   This research project focuses on cell-permeable prodrugs of the LIPG inhibitor XEN445.
3. MII Xue (co-PI) 11/10/2021 – 10/10/2022
   Maryland Innovation Initiative grant
   Project Title: "Novel anti-proteotoxicity therapeutic agents targeting protein methylation: Applications for Neurodegenerative Diseases"
   $115,000 direct cost to the Xue Lab
   This research focuses on the synthesis and biological evaluation of novel L3MBTL1 inhibitors.
4. MII Xue (co-PI) 9/10/2021 – 7/10/2022
   Maryland Innovation Initiative grant
   Project Title: "Novel Axin Stabilizer YA6060 is a Promising Therapy for NASH"

This research focuses on the synthesis and biological evaluation of novel Wnt signaling inhibitor YA6060 for the treatemt of NASH.

5. NEXUS Sub Xue (PI) 10/1/2020 – 06/30/2021
Johns Hopkins University $45,000
Developing Novel Drugs for Therapeutic Targets in Neurodegeneration
The goal of our research is to synthesize and test a series of UNC669 analogs as potential therapeutic candidates for neurodegenerative diseases.

6. NIH R21 Xue (PI) 1/1/2021 – 12/31/2023
1.0 calendar
University of Maryland Baltimore $424,875
Pseudomonas aeruginosa heme sensing inhibitors targeting HasAp
The goal of our research is to synthesize and test a series of GaSal analogs using established assays, to identify, validate, and characterize potent inhibitors of heme signaling and iron homeostasis.

7. MII Xue (PI) 12/10/2020 – 11/10/2021
Maryland Innovation Initiative grant
Project Title: "Antipseudomonal Agent GalSal: A Dual Inhibitor of Pseudomonas aeruginosa Heme Sensing and Iron Uptake"
$115,000 direct cost to the Xue Lab
This research focuses on the synthesis and biological evaluation of novel HasAp inhibitor GalSal as a therapeutic agent for Pseudomonas infections.
Role: PI

8. NSF Sub Xue (PI) 06/01/2019-05/31/2023
0.6 calendar
The University of Texas at Austin $203,385
Developing switchable electrophiles as specific covalent protein modifiers
The goal of our research is to develop novel selective probes that covalently modify proteins DDAH or BCL6 using the switchable electrophiles such as halopyridines. The availability of these probes will help understand the associated biochemical mechanisms and to better develop new therapeutics.

9. MII Xue (PI) 10/01/2018 – 7/31/2019
Maryland Innovation Initiative grant
Project Title: "YW2065 with Dual Activities of Wnt/β-catenin Inhibition and AMPK Activation for Colorectal Cancer (CRC)"
$115,000 direct cost to the Xue and Shu Labs
This research focuses on the synthesis and biological evaluation of novel Axin stabilizers as a therapeutic agent for CRC.
Role: Co-PI

10. MII Xue (Co-PI) 07/01/2018 – 04/30/2019
Maryland Innovation Initiative grant
Project Title: "Developing DL5016 as an enhancer for cyclophosphamide-based chemotherapeutics"
$115,000 direct cost to the Xue and Wang Labs
This research focuses on the synthesis and biological evaluation of novel hCAR activators as a combination agent for cyclophosphamide
Role: Co-PI

11. Waxman_ MacKerell (PI) 08/01/2014 – 06/30/2024
The Samuel Waxman Cancer Research Foundation
Project Title: "Small molecule BCL6 BTB domain inhibitors for DLBCL"

$65,118 direct cost the Xue Lab
This research centers upon the development of small molecule inhibitors of the BCL6 BTB domain as treatment for DLBCL
Role: Co-I

Other Completed Grants:

1. Center for AIDS Research Xue (Co-PI) 08/01/2017 – 09/30/2018
2017 NHP Pilot Grant Program
Project Title: "Pilot study to establish anti-Bcl-6 FX1 as an anti-HIV/SIV strategy by limiting SIV retention in germinal centers and replication in T follicular helper cells following ART-suppression"
$10,000 direct cost to the Xue Lab
This research centers upon the development of combination anti-HIV therapy using BCL6 BTB domain inhibitor FX1 and ART.
Role: Co-PI

2. LLS Melnick (PI) 12/01/2015 – 11/30/2018
Leukemia & Lymphoma Society
Project Title: "Therapeutic targeting of the BCL6 oncoprotein"
$410,463 direct cost to the Xue Lab
This research centers upon the development of small molecule inhibitors of the BCL6 BTB domain as treatment for DLBCL
Role: Co-I

3. 1R41AI113998-01A1 Xue (PI, subcontract) 04/01/2015 – 03/31/2019
NIH
Project Title: "Selective inhibitors of heme transporters as antiparasitic agents"
$137,256 direct cost the Xue Lab
This research centers upon the development of small molecule antagonists of the heme transporters as treatment for parasitic diseases
Role: Sub-award PI

4. AACR Career Development Awards 00167155 Xue (PI) 12/01/2015 – 11/30/2017
American Association for Cancer Research
Project Title: "BCL6 BTB domain inhibitors for triple-negative breast cancer"
$138,000 direct cost to the Xue Lab
This research centers upon the development of small molecule inhibitors of the BCL6 BTB domain as treatment for breast cancer
Role: PI

5. UM Ventures Xue (PI) 05/16/2016 – 05/15/2017
UM Venture Seed Grant Program
Project Title: "WNT signaling pathway inhibitors for treatment of diseases"
$15,000 direct cost the Xue Lab
This research centers upon the development of small molecule WNT inhibitors domain with improved aqueous solubility
Role: PI

6. ENABLE_ Wilks (PI) 08/01/2014 – 07/31/2015
European Gram-negative Antibacterial Engine Program

Project Title: "Heme utilization by gram negative pathogens"
This research centers upon the development of small molecule inhibitors of the bacterial HemO as treatment for bacterial infections
Role: Co-I

7. Janssen Research Grant Melnick (PI) 09/01/2014 – 08/31/2015
Janssen Pharmaceutics
Project Title: "Small molecule BCL6 BTB domain inhibitors"
$41,608 direct cost the Xue Lab
This research centers upon the development of small molecule inhibitors of the BCL6 BTB domain as treatment for DLBCL
Role: Co-I

8. LRF Research Grant Xue (PI) 07/01/2014 – 06/30/2015
Leukemia Research Foundation Research Grant
Project Title: "Small molecule BCL6 inhibitors for diffuse large B-cell lymphoma (DLBCL)"
$100,000 direct cost the Xue Lab
This research centers upon the development of small molecule inhibitors of the BCL6 BTB domain as treatment for DLBCL
Role: PI

9. IDR_224-13 2013 Xue (PI) 07/01/2013 – 06/30/2015
University of Maryland Pilot and Exploratory Interdisciplinary Research (IDR) Award
Project Title: "Positive allosteric modulators (PAMs) of metabotropic glutamate receptor 5 (mGluR5) for traumatic brain injury (TBI)"
$75,000 direct cost the Xue Lab
This research centers upon the development of small molecule PAMs of mGluR5 as delayed treatment of TBI
Role: PI

10. ACS-IRG 10009632 Xue (PI) 03/01/2012 – 02/28/2013
American Cancer Society Institutional Research Grant (ACS-IRG)
Project Title: "Development of novel Kaiso inhibitors as drug candidates for human colon cancer"
$30,000 direct cost the Xue Lab
This research focuses on the development of small molecule inhibitors of Kaiso as a novel strategy to treat human colon cancer
Role: PI

11. mGluR5 Faden (PI) 09/01/2011 – 08/31/2013
University of Maryland School of Medicine
Project Title: "Development of mGluR5 activators as drug candidates for traumatic brain injury"
$150,000 direct cost the Xue Lab
This research focuses on the development of small molecule activators of the metabotropic glutamate receptor 5 (mGluR5) as potential treatment of traumatic brain injury (TBI)
Role: Co-I

Grants/Fellowships to Graduate Students:

1. Garrick Centola: PSC Fellowship Award. 9/1/20 – 8/31/21
2. Elizabeth Robinson: CBI Fellowship. 7/1/19 – 6/30/21

3. Geoffrey Heinzl: AFPE Fellowship. 7/1/13 – 6/30/15
4. Geoffrey Heinzl: ACS MedChem Fellowship. American Chemical Society. 07/1/14 – 6/30/15

CURRENT COLLABORATORS

UMB Collaborators

1. Alexander MacKerell: *BCL6 inhibitors, HemO inhibitors, HasAp inhibitors, hCAR activators*
2. Angela Wilks: *HemO inhibitors, HasAp inhibitors*
3. Yan Shu: *Axin stabilizers, 5FU prodrugs*
4. Hongbing Wang: *hCAR activators, Nrf2 activators*
5. James Polli: *Bile acid drug-delivery systems*
6. Iqbal Hamza (UMB-SOM): *heme transporter inhibitors*
7. Richard Zhao (UMB-SOM): *HTS in drug development*

External Collaborators

1. Ari Melnick (Cornell): *BCL6 inhibitors*
2. Menghang Xia (NCATS): *Wnt inhibitors, hCAR activators, AChE inhibitors*
3. Walt Fast (UT Austin): *p-halopyridines*
4. Dali Li (Loyola University at Chicago): *covalent BCL6 inhibitors*
5. Bill Lanzilotta (Georgia): *Aza-Sam derivatives*
6. Leandro Cerchiette (Cornell): *Tubulin inhibitors, BCL6 inhibitors for lung cancer*
7. Jiou Wang (JHU): *Small molecule therapeutics for neurodegenerative diseases*
8. Fengyi Wan (JHU): *Wnt inhibitors*
9. Qun Zhou (VA): *LIPS inhibitors*
10. Bin Gao (NIAAA): *Hepatoselective ALDH2 inhibitors*